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The Journal of Associated Medical Sciences belongs to Faculty of Associated Medical Sciences (AMS), Chiang Mai University, Thailand. The journal specifically aims to provide the platform for medical technologists, physical therapists, occupational therapists, radiologic technologists, speech-language pathologists and other related professionals to distribute, share, discuss their research findings, inventions, and innovations in the areas of:

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2. Physical Therapy
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4. Radiologic Technology
5. Communication Disorders
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- **Original articles** must not exceed 15 journal pages (not more than 3,500 words), including 6 tables/figures, and 40 reference (maximum 40, recent and relevant).
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Structure of personal narratives in Thai children aged 4 to 6 years old

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ABSTRACT

Background: Understanding children's narratives is crucial as it represents language capacity in a naturalistic context and also relates to children's academic success. However, studies showed that narratives vary not only with age but also in content and structure across cultures.

Objectives: To study and compare components and patterns of personal narratives in Thai children aged 4-6 years old. Also, to find narrative structure differences between genders.

Materials and methods: Stories of past experiences were elicited from 86 participants aged 4-6 years old. The longest narratives from each participant were analyzed in terms of both narrative components and patterns by using high-point analysis. Comparisons were then drawn for the proportions and differences in narrative structure between age groups and between genders.

Results: For narrative components, Thai children told complicating action most frequently. With age, the use of resolution increased significantly from 4-6 years old. For narrative patterns, chronological patterns were found commonly at age 4. Moreover, the incidence of classic patterns rose significantly between the ages of 4 and 6 and reached the highest proportion in usage at ages 5 and 6. No gender difference was found in the narrative structure.

Conclusion: Thai children's narrative structure was presented in this study. The abilities to range events in sequence and resolve the high-point of narratives were found more commonly with their increasing age.

Introduction

Narration is an activity of life that people use to express their identity and personal experiences with others.[1-3] This skill is developed from an early age. Since children are 2 years old, they learn to talk about their real past events in conversation with their parents.[2] Through daily talking, the ways parents support and provide information to their children lead to the improvement of the children's narrative skills and also influence the style of their narration later.[4] A story that tells about people's own experiences is called a personal narrative. This is the earliest narrative that children use,[5] and it is still used most frequently when they are in preschool to interact with others.[5,6] Even when becoming adults, this kind of narrative is necessary for communication such as for medical or legal situations.[7] Therefore, personal narratives are important throughout the life span.

Moreover, narratives are related to literacy ability. This is because a narrative is created by matching the order of the narratives and the order of real past events.[8] It, therefore, links to decontextualized language skill. Many research studies approved this important relevance. Parents and children

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reminiscing about experiences affected their children's later language ability at kindergarten.[9] Also, oral narrative skills in preschool children correlated with academic performance when they were in primary school.[10,11] Thus, children's narratives can be a predictor of literacy achievement.

To understand children's narratives, not only vocabulary or grammar usage are necessary, but assessing its structure is also essential. Atypical narrative is not related to the abilities of phonology, semantics, or syntax.[7] Therefore, it is crucial to explore the narrative structure simultaneously with other linguistic features. For these reasons, assessing children's narrative structure plays an important role in monitoring and preventing language delays in children. Presently, there are various principles for assessing the macrostructure of narrative and one of the wide uses across the world is called high-point analysis.

High-point analysis.

The high-point analysis is a famously used approach for studying personal narrative macrostructure. This method was first described by Labov and then was later adapted by Peterson and McCabe[12] for studying personal narratives in European North American children aged 4-9 years old. High-point analysis has been found capable of analyzing personal narratives in children appropriately in several populations such as North American, African American, Chinese, Taiwanese, and Korean.[12-16]

Based on Peterson and McCabe study,[12] narrative clauses can be categorized into: (1) *appendages*: Superfluous niceties of narrative comments that are presented at the beginning or the end of the narrative. Four types of this component are: 1) *abstract*: Summaries of the whole story that appear at the beginning; 2) *attention-getter*: Attempts to get the listeners' attention; 3) *prologue*: Statements at the beginning of the story that presents the ending significance, and 4) *coda*: Ending signals of the narrative. These are followed by: (2) *orientation*: Statements that provide the background information including participants, location, time, and other conditions that help listeners understand the narrative more clearly; (3) *complicating action*: The series of specific events that occur until reaching the high-point; (4) *evaluation*: Statements that let listeners know what the narrator thinks about the events that occurred, and (5) *resolution*: Specific events after the high-point that appear to resolve the crisis action.

Additionally, Peterson and McCabe[12] suggested further patterns of the narratives which were subsequently adjusted to be a clinical research tool for speech-language pathologists.[5] Narrative patterns can be categorized into seven patterns as follows[5,12]: (1) *one-event narrative*: The narrative has only a single event; (2) *two-event narrative*: The narrative has two past events; (3) *miscellaneous narrative*: The narrative has more than two past events but there is no logical or causal sequence of these events in the real world; (4) *leapfrog narrative*: The narrative has more than two complicating actions from a single experience. However, they are not in chronological order. Also, the narrator may jump to another event by leaving out major events which leads to difficulty in understanding for listeners; (5) *chronological narrative*: The narrative is a description of successive events. No high-point is presented; (6) *end-at-the-high-point narrative*: The narrative has complicating actions ordered chronologically until reaching the high-point, but no resolution at the end, and (7) *classic narrative*: The narrative has a well-ordered sequence of events that build to the high-point, and then resolves it successively. At the high-point, the narrator may dwell on evaluation.

As children continually develop their narrative ability with age, Peterson and McCabe[12] described the development of narrative macrostructure whereby children of an early age produced two-event narratives as their longest narratives. When children were 4 years old, they were then better able to combine several events but missed some important events in the form of the leapfrog narrative. At age 5, children can range events in order to reach the high-point in the form of end-at-the-high-point narrative. Lastly, when children were 6 years old and older, they were skillful in producing classic narratives. It is, therefore, evident that age affects children's narrative structure.

However, age is not the only factor affecting the narrative structure, previous studies have shown that social class[17] and maternal narrative supports[18] are also influenced. Among these several factors, one of the greatest impacts on a narrative that can be marked is culture.

Cultural differences

There were several cross-cultural studies that showed the different eliciting strategies parents used for everyday talking with their children.[19,20] Besides, the emphasis on children's narratives in the classroom is also distinct between societies.[21] These resulted in the difference in children's narratives across populations.[22-24] Comparisons across cultures about children's narrative development have been studied widely. Elaborative narratives with highly-expressed self-evaluation were commonly seen in individualistic cultures such as North American culture, reflecting the encouragement to talk more about their past and feelings that their parents provided.[2] On the other hand, collectivist cultures such as Asians have lower expression and provide less information as it is assumed that knowledge is shared in their populations.[25] For example, Minami[26] found that Japanese mothers requested less description and provided less evaluation but more frequent turn exchange through conversation than the US mothers; Japanese children consequently produced fewer utterances per turn in their talking.

Within Asian cultures, there are also studies showing that even though they shared some characteristics, there is a distinctive style in which each of the narratives was presented. Japanese children, as in Minami's study,[27] tell succinct narratives which have a collection of three experiences. For Chinese children, Zhang *et al*.[14] found that they were experts in using complicating action, orientation, and evaluation that can lead to longer narratives with age, and also found that chronological patterns were used mostly in Chinese children aged 4-6 years old. Moreover, Lai *et al*.[15] compared preschool narratives between Korean and Taiwanese children aged 3-5 years old, and the results showed that narratives from Taiwanese children contained more internal state terms than those from Korean children, while Korean children notably developed their narrative structure much more than Taiwanese

children at the age of 5.

Therefore, it is important to consider cultural narrative characteristics to not misunderstand cultural differences and language impairment that may lead to wrong assessment results and inappropriate intervention plans.[5,22,28,29]

That is also a collectivist culture. Conversations between Thai caregivers and their children were found to be short and unelaborated but valued in temporal contextual information compared to English-speaking caregivers. There was then a prediction of Thai children's narratives that they would be succinct.[25,30] If this assumption was proved along with a better understanding of Thai children's narrative characteristics, it would help speech-language pathologists and other pediatric specialists find the best and most applicable interventions for children.

Current study

In the current study, the researcher investigated personal narratives in Thai children aged 4 to 6 years old to find the difference in narrative structure between age groups in terms of both narrative components and narrative patterns. It was hypothesized that children at different ages would produce different narrative structures. Furthermore, gender comparisons were also conducted to find any differences in the narrative structure.

Materials and methods

Participants

A total of 86 participants were randomized from three public schools in Bangkok, Thailand, which were also randomly selected. All participants were recruited for this study by the following criteria: (1) aged between 4-6; 11 years old (2) no report for speech and language delay from their parents; (3) Thai citizen; (4) passed the UTAH screening test for children aged 2-9 years old (Thai version); (5) use Thai as their mother tongue, and (6) parents consented to participate in this study. There were two exclusion criteria: (1) cannot cooperate, and (2) respond by telling fewer than 3 stories.

The parents of participants were mostly not university graduates, had family income between 10,000 to 30,000 baht/month, and were company employees or self-employed.

Table 1 Demographic information of the participants.

Age groups (years)	Boys (number)	Girls (number)	Age range (months)	Mean age (months)	Median age (months)
4	11	15	55-59	58.13	58
5	15	15	60-71	65.10	65.5
6	15	15	73-83	76.97	76

Procedures

To collect narrative samples, one appropriate method is to use a story prompt which is a brief story of the interlocutor's experience to help participants recall their own experiences more easily. Therefore, before the interviews, 16 story prompts were created by the researcher on several topics; topics that can help to elicit complex narratives from children such as visiting a doctor[31] or misbehaviors,[23] and topics that were found in discussions between Thai caregivers and children such as weekend activities or looking after younger siblings.[30] These story prompts were then scored to find the content validity by 5 experts who had more than 15 years of experience working with children; 1 preschool teacher, 1 clinical psychologist, and 3 speech-language pathologists. Consequently, the best 8 story prompts were chosen and tried in conversation with 18 children; 6 children for each age group, and all of them studied in the same schools as the participants. The 5 story prompts that resulted in children mostly telling a long narrative in return were finally selected to use in this study.

The narrative sample collecting process was conducted in a quiet room in the schools where the participants studied. The interviewing process started by building a rapport between the researcher and each participant by using toys, drawing, and talking. After that, the researcher used a conversational map[5] to collect the participants' narratives. Each story prompt was told and participants were then asked to share their own related experiences. After that, the researcher repeated this process until all story prompts were used. During this period, the researcher provided neutral sub prompts such as "Ahh", "What's next?", "Anything else?" or just repeated their words to motivate participants to continue their stories without guiding them about what they should tell. The interview with each participant was between 15 to 20 minutes. After finishing the conversations, participants received a toy and colored pencils as rewards.

All interviews were recorded in audio. Because the length of narratives indicates their complexity, the longest narrative from each participant was chosen to be the narrative sample for this study. A total of 86 narrative samples were transcribed and divided into clauses by these two measures: (1) when the narrators paused their stories, and (2) if the following utterances show connections of consequence, contrast, reason, or time. These criteria were chosen to fit the style of the Thai language, in which utterances were arranged in sequence.[32]

All narrative samples had their structure in both components and patterns determined by the researcher. Each clause was analyzed to evaluate what type of narrative component it was: appendages, orientation, complicating action, evaluation, or resolution. Then, the whole narratives were scored on the basis of their narrative patterns:[33] a one-event narrative (1 point); a two-event narrative (2 points); a miscellaneous narrative (3 points); a leapfrog narrative (4 points); a chronological narrative (5 points); an end-at-the-high-point narrative (6 points), or a classic narrative (7 points). Meanwhile, 20% of narrative samples (18 narratives) were randomized and sent to another speech-language pathologist who specialized in paediatric speech-language therapy for over 15 years to score the structure as well. After comparing the score results between the researcher and the speech-language pathologist, the results that were not the same were then re-evaluated to

reach a consensus and were checked a second time with another researcher. The rest of the narrative samples were then scored by referring to the consensus guidelines.

Results

Narrative components

All types of narrative components were found in the narrative samples, but the subtypes of appendages were however found only as abstract and coda. The examples from the narrative samples are presented as follows: (1) appendages: abstract "น้องหนูโดนเข็มฉีดยาเพราะน้องหนูโดนหมากัด" (My sister was injected because she was bitten by a dog), coda "ก็แค่นี้" (That's all.); (2) orientation "ตอนที่มันปิดเทอมใหญ่ (when there was a school break); (3) complicating action "แล้วพี่ก็หยุดแล้วมันทับนิ้วโป้งหนู" (Then he stopped and it hit my thumb); (4) evaluation "เจ็บมากเลยค่ะ" (That's really hurt), and (5) resolution "แล้วจากนั้นก็ไปรักษากับพ่อ พ่อรักษาให้ก็หายเลย" (After that I was cured with dad, he cured then I got well).

Table 2 The number of clauses in each narrative component, the total number of clauses, and the mean of clauses in each age group.

Narrative Components	Number of clauses		
	Age 4 (n=26)	Age 5 (n=30)	Age 6 (n=30)
Appendages	22	18	32
Orientation	74	86	92
Complicating action	125	196	195
Evaluation	85	80	130
Resolution	5	31	30
Total number of clauses	311	411	479
Mean of clauses	12	13.7	16

All narrative components were calculated and shown in Table 2. From the mean of clauses, it can be seen that the means increased through averages of 12, 13.7, and 16 clauses in the ages 4, 5, and 6 sequentially. However, the Kruskal-Wallis test in Table 3 showed that there was no difference between each age group.

Table 3 Means, standard deviations, mean ranks, and the Kruskal-Wallis test summaries for the total number of clauses in each age group.

Age groups	Mean	SD	Median	Mean rank	Kruskal-Wallis Chi-square	df	Asymp sig.
4	12	7.39	10	35.79	5.209	2	0.074
5	13.7	7.46	10	42.73			
6	16	8.24	13	50.96			

***Note**: Asymp sig.: asymptotic significance, df: degree of difference.*

Each narrative component was then calculated separately. Because both the number of each age group and the number of clauses from each narrative sample were not equal, the data were converted to the mean proportion. Figure 1 showed that Thai children aged 4-6 had the same three highest proportions in the use of narrative components: complicating action, evaluation, and orientation respectively. By this, complicating action was by far the most frequently used.

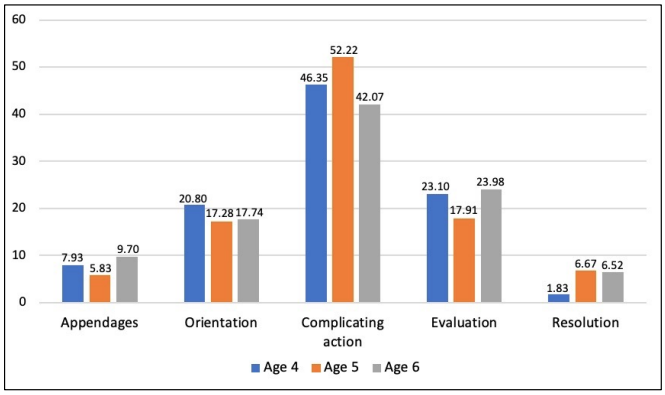

***Figure 1**. Mean proportion of narrative components in age groups 4-6 (%).*

To compare each narrative component between age groups, the Kruskal-Wallis tests were conducted and shown in Table 4. Across all age groups, only resolution indicated a statistically significant difference (p=0.012*). Pairwise comparisons were then analyzed and shown in Table 5. There remained a statistical significance only between ages 4 and 6 (p=0.010*).

Narrative patterns

To understand the use of narrative patterns in Thai children aged 4-6 years old, the proportion of each type of narrative pattern from the different age groups was assessed as shown in Figure 2.

From Figure 2, children aged 4 most used chronological patterns at 30.77%, followed by leapfrog patterns at 23.08%. Two-events and end-at-the-high-point patterns were equal at 15.39% while classic patterns were at 11.54% and miscellaneous patterns were lowest at 3.85%. For children aged 5, the highest proportion for the use of narrative components was observed for the classic pattern at 33.33%. Leapfrog and chronological patterns were at the second rank at 26.67%. End-at-the-high-point patterns were markedly lower at 10% and miscellaneous patterns were minimally presented at 3.33%. Moreover, two-events patterns were not presented at this age. Narrative patterns in children aged 6 showed different proportions in each type. Classic patterns showed by far the highest use at 50% while end-at-the-high-point patterns took second place with less than half of that proportion at 23.33%. Next was chronological patterns at 10% and then two-event and leapfrog patterns at 6.67%. The lowest proportion at 3.33% was for miscellaneous patterns. It was also notable that there was no one-event pattern in any age group.

Despite the trends that were seen in Figure 2, the Kruskal-Wallis test in Table 6 showed that there was no statistically significant difference in any narrative patterns across age groups except for the classic pattern (p=0.010*). Pairwise comparisons then showed that a statistically significant difference was found between ages 4 and 6 (p=0.007**) but there was no difference between other groups as shown in Table 7.

Comparisons of narrative components and patterns between genders were conducted. Table 8 showed the results from the Kruskal-Wallis tests revealing that there was no gender difference for all narrative components.

In Table 9, it was also seen that there was no difference between genders in narrative patterns by using the Kruskal-Wallis tests.

Table 4 Means, standard deviations, mean ranks, and the Kruskal-Wallis test summaries for narrative components in each age group.

Narrative Components	Age groups	Mean	SD	Median	Mean rank	Kruskal-Wallis Chi-square	df	Asymp sig.
Appendages	4	0.85	0.92	1	43.38	3.861	2	0.145
	5	0.60	0.72	0	37.63			
	6	1.07	0.94	1	49.47			
Orientation	4	2.85	3.34	2	42.37	0.244	2	0.885
	5	2.87	3.46	2	42.70			
	6	3.07	3.16	2	45.28			
Complicating action	4	4.81	2.43	4	35.27	4.132	2	0.127
	5	6.53	3.87	5.5	46.65			
	6	6.50	4.07	5	47.48			
Evaluation	4	3.27	3.76	2	42.50	1.580	2	0.454
	5	2.67	2.88	2	40.02			
	6	4.33	4.30	2.5	47.85			
Resolution	4	0.19	0.63	0	34.06	8.864	2	0.012*
	5	1.03	2.01	0	44.73			
	6	1.00	1.31	0.5	50.45			

***Note**: *p<0.05, Asymp sig.: asymptotic significance, df: degree of difference.*

Table 5 Pairwise comparisons between age groups in narrative components.

Pairs of age group	Test statistic	SE	Std. test statistic	Adj. sig.
Age 4-5	-10.676	5.557	-1.921	0.164
Age 4-6	-16.392	5.557	-2.950	0.010*
Age 5-6	-5.717	5.355	-1.068	0.857

***Note**: *p<0.05, Adj. sig.: adjusted significance, Asymp sig.: asymptotic significance, Std. test statistic: standard test statistic.*

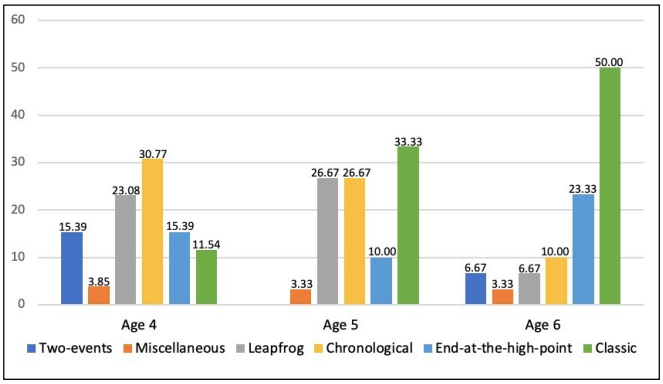

***Figure 2**. Proportion of narrative patterns in age groups 4-6 (%).*

Table 6 Mean ranks, and the Kruskal-Wallis test summaries for narrative patterns in each age group.

Narrative Patterns	Age groups	Mean rank	Kruskal-Wallis Chi-square	df	Asymp sig.
One-event**	4	43.50	0.000	2	1.000
	5	43.50			
	6	43.50			
Two-events	4	47.12	5.027	2	0.081
	5	40.50			
	6	43.37			
Miscellaneous	4	43.65	0.014	2	0.993
	5	43.43			
	6	43.43			
Leapfrog	4	45.42	4.403	2	0.111
	5	46.97			
	6	38.37			
Chronological	4	47.23	4.004	2	0.135
	5	45.47			
	6	38.30			
End-at-the-high-point	4	43.12	1.955	2	0.376
	5	40.80			
	6	46.53			
Classic	4	34.46	9.287	2	0.010*
	5	43.83			
	6	51.00			

***Note**: *p<0.05, **No one-event pattern was found in this study, df: degree of difference, Asymp sig.: asymptotic significance, df: degree of difference.*

Table 7 Pairwise comparisons between age groups in narrative patterns.

Pairs of age group	Test statistic	SE	Std. test statistic	Adj. sig.
Age 4-5	-9.372	5.431	-1.726	0.253
Age 4-6	-16.538	5.431	-3.045	0.007**
Age 5-6	-7.167	5.233	-1.369	0.513

***Note**: **p<0.01, SE: standard error, Std. test statistic: standard test statistic, Adjusted significance.*

Table 8 Gender differences in narrative components.

Narrative Components	Gender	Mean	SD	Median	Mean rank	Kruskal-Wallis Chi-square	df	Asymp sig.
Appendages	male	0.83	0.97	1	42.34	0.193	1	0.660
	female	0.84	0.80	1	44.56			
Orientation	male	3.17	3.02	2	48.10	2.727	1	0.099
	female	2.71	3.53	1	39.31			
Complicating action	male	5.76	3.36	5	42.72	0.078	1	0.780
	female	6.22	3.87	5	44.21			
Evaluation	male	3.78	3.77	2	46.07	0.856	1	0.355
	female	3.11	3.68	2	41.16			
Resolution	male	0.59	1.10	0	41.83	0.508	1	0.476
	female	0.93	1.78	0	45.02			

***Note**: SD: standard deviation, df: degree of difference, Asymp sig.: asymptotic significance.*

Table 9 Gender differences in narrative patterns.

Narrative Patterns	Gender	Mean rank	Kruskal-Wallis Chi-square	df	Asymp sig.
One-event	male	43.50	0.000	1	1.000
	female	43.50			
Two-events	male	43.65	0.014	1	0.906
	female	43.37			
Miscellaneous	male	45.15	3.372	1	0.066
	female	42.00			
Leapfrog	male	41.79	0.806	1	0.369
	female	45.06			
Chronological	male	42.39	0.300	1	0.584
	female	44.51			
End-at-the-high-point	male	45.94	1.828	1	0.176
	female	41.28			
Classic	male	42.09	0.382	1	0.537
	female	44.79			

***Note**: df: degree of difference, Asymp sig.: asymptotic significance.*

Discussion

From the results of this study, Thai children's narrative structure develops with age in both narrative components and patterns. However, the statistical analysis showed almost no statistically significant difference between age groups, although it provided trends as noted in the following discussion.

Children's narratives can be predicted from how caregivers elicited narratives and what they focused on when talking with their children.[4] For Thais, conversations between caregivers and their children were concise.[25,30] The results of the current study corresponded with these findings that the length of children's personal narratives, even though becoming longer by mean values in older children,

was still succinct and showed no difference between age groups (as in Table 3).

All narrative components can be found in Thai children's personal narratives from the age of 4 years old. For all age groups, complicating action, which is the backbone of narratives, was by far the most widely used (Figure 1). This is similar to previous studies such as in North American[12] and Chinese children's narratives[14] whereby they also use complicating action as the most frequent narrative component. Moreover, when comparing between age groups it is shown that there is a significant difference in resolution across ages 4 and 6 (p=0.010*). For resolution, it is a narrative component that occurs after the high-point; therefore its increasing use correlated with the more frequent occurrence of the classic pattern which is generally found at the age of around 6 in children.

Moreover, even though previous studies have shown that Asian children used evaluation less than children from western culture,[28,30] it is interesting that evaluation was the second most frequently used of the narrative components in this study (Figure 1). The reason might be related to the topics of the story prompts which were used when collecting the narrative samples. As in previous studies, topics about children's misbehaviors had matchable content to the high-point structure; there are specific events that reach the climax and also give some resolution at the end.[23] Therefore, the story prompts' topics might affect the findings about the proportion of usage of evaluation in this study.

In terms of narrative patterns, Thai children also produced more complex narrative patterns when they got older. Chronological patterns were commonly found at age 4 in Thais. This is similar to narrative patterns of North American,[12] Latino,[23] and Chinese children[14] at the same age. Moreover, leapfrog patterns which were also normally used at this age in North American[12] and Taiwanese children[15] were also presented as the second rank of the proportion of usage in Thais. This resulted in the conclusion that the developmental level of narrative patterns in Thai children aged 4 resembled previous studies. At age 5, Thai children mostly used classic patterns; this narrative pattern was more frequently used, notably from the age of 4 (from 11.54% to 33.33%), and this development was also obviously seen when Thai children were aged 6 as half of the narrative patterns by proportion were then classic patterns. Furthermore, comparisons between age groups showed significant differences between the ages 4 and 6 (p=0.007**). This indicated that children were better able to resolve their stories with age, and the current finding was related to prior studies in which children produced more classic patterns at older ages.[12,14] On the contrary, it can be seen that simple patterns were found less along with children's growth. Two-events patterns were presented at 15.39% at age 4 and decreased to 6.67% at age 6. The reduced use of this pattern is related to prior studies in Chinese,[14] Taiwanese, and Korean children[15] which also had decreased trends when children grow up. However, it is notable that this pattern was not shown at age 5 in Thai children in this study. The reason for this might come from the small number of participants and the research procedure that required at least three narrative samples from each child which resulted in more opportunities to produce their best narrative.

Gender difference analysis was also included in this study. The results, however, presented no difference in terms of both narrative components and narrative patterns, and this conformed to several earlier studies that confirmed that gender did not affect the narrative structure.[12,14] This might be related to technological advancement today that supports daily communication systems and also the improvement of curricula in the classroom, resulting in gender equality in terms of learning opportunities for children.[34]

One more thing that might affect the results was the social class of the participants. In this study, most of the parents were of similar status, so the results reflected only the children's personal narrative structure in this particular group. Previous studies have shown that children of higher status had better narration skills.[17,35] Therefore, if collecting further narrative samples from other classes, longer or more complicated narrative structures might be seen.

Limitations of the Study

According to the results, even though participants in this study were separated by their age, the mean and median values of age in months indicated that the gaps between groups were not wide. The reason for this was the Covid-19 situation that resulted in limiting the number of appropriately-aged participants. If the ages of the participants were more different and there were also more participants, the distinct development of their narrative structure would be more clearly observed.

Moreover, despite the overall narrative structure in Thai children presented, the different concerns in types of contextual information and evaluation in children's narratives have not yet been distinguished. Prior studies showed that there were different preferences in children's group comparisons.[12,36,37] Thus, future research is needed for a deeper understanding across both age and gender.

Conclusion

In Thai children's narratives, the sequence of events was emphasized. They used complicating action most frequently and had significantly increasing use of resolution with age. These corresponded to their narrative patterns. At age 4, Thai children commonly used chronological patterns, while at ages 5 and 6 they mostly used classic patterns. Furthermore, the narrative structure between genders, as predicted, had no difference presented.

Conflicts of interest

The authors declared that no competing interests existed at the time of publication.

Ethical approval

This study was approved by the Research Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University (Approval ID: AMSEC-62EX-047).

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Depression, anxiety, and stress in Health care workers due to COVID-19 pandemic in hospitals of Odisha: A Cross-sectional survey

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ABSTRACT

Background: COVID-19, an unprecedented pandemic significantly affects psychologically healthcare workers (HCWs). The World Health Organization has also announced the pandemic as a Global Public Health Crisis. Priority to observe psychological effects was critical to understanding the various factors and delivering a tailored approach to treatment. This study aims to analyse the prevalence and severity of depression, anxiety, and stress amongst HCWs in Odisha during the pandemic.

Materials and methods: A cross-sectional, observational, questionnaire-based online study was conducted. A total of 300 HCWs participated. The collection of data was done online through a self-administered validated depression, anxiety, and stress (DASS-21) questionnaire designed in Google form. The questionnaire has three sections, consent form, demographic characteristics, and DASS-21. For analysis of categorical variables descriptive statistics, Chi-square test, and Binomial test were used, and for continuous variables, Kruskal Wallis test & Mann-Whitney test were used and '*p*'<0.05 was considered significant.

Results: In this study, respondents were young (63.7%) and the majority were females (61.7%). Doctors constitute 57%, nurses 35%, dentist 17.7% and pharmacists 7% ($p<0.001$). The majority work in non-government sectors ($p<0.001$), having 1-5 years of experience ($p<0.001$). As many as 42.7% of HCWs have depression, 53.7% anxiety, and 13.3% stress. The professional category has a significant association with depression, anxiety, stress, and overall, DAS score ($p<0.01$). Doctors have the highest level of depression, anxiety, stress, and overall, DAS score, followed by nurses, dentists, and pharmacists. Gender played a significant association with anxiety and stress. Females have a significantly higher level of anxiety and stress ($p<0.05$).

Conclusion: The present study revealed a higher proportion of depression, anxiety, and stress in HCWs. Early screening for detecting mental health issues should be initiated for HCWs who are being exposed repeatedly. Hence, group-specific need-based psychotherapy is critical during the pandemic.

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Introduction

The coronavirus disease (COVID-19) pandemic, which originated in the city of Wuhan, China, in December 2019 quickly grappled the whole world and was declared a pandemic by WHO, on March 2020[1] impacting health care workers to a major extent. The disease spread quickly to various countries and as of 22nd June 2022, in India, there were 4.3 crores confirmed cases and 5.25 lakh deaths.[2] Crisis of healthcare resources and fear of exposure led to significant levels of stress, anxiety, and depression. Public Health Emergency of International Concern (PHEIC) like the COVID-19 pandemic can also pose a significant mental health risk to common people of different age groups and other frontline workers. The pandemic was further complicated by unprepared health infrastructure and associated factors like lack of training for infection control and the stigma of getting infected. This situation exposed them to higher stress levels and apprehension. History of any infectious disease like the Ebola outbreak, or HIV pandemic, suggests that even after 1 year of outbreak people continue to experience symptoms of traumatic injury.[3,4]

WHO declared the outbreak of COVID-19 to be a pandemic,[4] with estimates of global mortality at 3.4%. There was panic amongst health care workers (HCWs) which led to stress and anxiety.[5,6] They were the only category who were working under pressure, with long shift times and lack of personal protective equipment (PPE), were in fear of transmitting the infection to their kith and kin and were at risk of self-exposure.[7] Besides the ongoing problem of exposure, avoidance of socializing and lack of coping strategies also bestowed negative effects on their mental health. The COVID-19 outbreak was an unprecedented scenario for many workers across the world. Many studies of healthcare workers in China reported psychological symptoms such as depression in 50%, anxiety in 45%, insomnia in 34%, and mental distress in 71.5%, especially among female nurses and frontline healthcare workers, who were directly involved in the management of patients with COVID-19.[8] A study done in Singapore, related to health care workers found 14.5% positive for anxiety, 8.9% for depression, 6.6% for stress, and 7.7% for clinical concern of post-traumatic stress disorder (PTSD).[9] The HCWs such as doctors, nurses, pharmacists, and other frontline workers were also affected psychologically. This caused personal and family life imbalance, and mental health issues, leading to perpetual depression, anxiety, and stress.[10,11] Due to lockdown, economic instability and shortage of essential medications predisposed them to psychological turmoil. The rising mortality rate has caused a severe negative effect on HCWs.[12,13] Transmission of the disease among HCWs is due to overcrowding, absence of isolation room facilities, environmental contamination, etc. During the COVID-19 pandemic, HCWs played a major role and pushed their limits every day. They bring in the frontline of the system and were bound to take the maximum brunt. The situation was further complicated due to complete uncertainty, unprepared health infrastructure, fear, anxiety, stigma, prejudice, and marginalization toward the disease.

A study in Korea assessed the total impact of the outbreak with Events Scale-Revised. They found that 51.5% had PTSD.[14]. One year after the SARS outbreak, a study found that health care workers that had survived a SARS infection still had elevated stress levels and psychological turmoil.[15] COVID-19 pandemic and post-covid complications have thrown serious challenges to healthcare professionals. This situation exposed them to a higher stress level, anxiety, and apprehension. Moreover, it affects the work output which, might affect the healthcare delivery system. There are few studies done on how COVID-19, affects health care workers' mental health.[16] The rapid escalation of COVID 19 reflected strong emotional stress on populations particularly healthcare workers (HCW) who were confronting huge physical and mental stressors in coping with the demanding crisis.[8]

Similarly, the primary endpoints of the multi-center study amongst healthcare workers in NHS hospitals in Lancashire revealed a marked prevalence of psychological impact such as depression (67%), moderate to severe anxiety (30%), and elevated levels of stress (moderate-severe) (73%) among HCWs during the peak of the Covid-19 pandemic in the region.[17,18]

Hence, the study was undertaken to assess depression, anxiety, and stress in these populations. Knowing the psychological impact of the COVID-19 outbreak among healthcare workers it is imperative to frame and monitor future guidelines for mental health, as well as ensure an optimal health care service. Our aim in this study was to assess the magnitude of impact on health care workers, including depression, anxiety, and stress, with environmental factors, demographic profile, and community stigmatization in different hospitals of Eastern India during the early phase of the pandemic. HCWs were acutely conscious of the infectivity of the virus and were distressed. Therefore, to decrease occupational hazards while commuting to work, after being exposed to the virus, appropriate guidelines should be implemented to reduce stress and anxiety. Occupational distress can be attenuated to some extent by social networking and support from friends, family members, and various healthcare stakeholders.

Materials and methods

Study design

This cross-sectional, observational, questionnaire-based online survey was conducted in November 2021 durin the period of the COVID 19 pandemic among health car workers working in various hospitals, clinics, and healt centers of Odisha, India, conducted by the Department o Pharmacology, IMS & SUM Hospital. The inclusion criteri were health care workers, including all cadres of doctors, nurses, and pharmacists working in tertiary care and variou other hospitals of Odisha, India with a willingness to tak part in the research, male/female, having social media accounts, conversant with the English language. The exclusion criteri for the study were those who responded outside the stud period, were not willing to take part in the research, ha no social media account, and were pilot study participants.

Depression, anxiety, stress-21 item (DASS-21 scale) questionnaire was designed in google form in English, an a link was shared with the WhatsApp group of HCWs. It

was also sent personally to all the HCWs in the contact list of the Investigators. Furthermore, these healthcare workers were requested to forward the link to their contacts (HCWs) i.e. snowballing sampling. The internal consistency reliability of the scale was acceptable to high, with a Cronbach Alpha of 0.72 for depression, 0.77 for anxiety, 0.70 for the stress subscale, and 0.88 for the overall scale.[18] The questionnaire has three sections: informed consent, demographic details, and DASS -21. The Likert scale was used to measure the response. The prevalence of depression, stress, and anxiety among the HCWs was analysed along with the factors responsible for the same.

The HCWs who clicked the link were directed to the first page of the google form, which contains information about the study. On providing the consent to take the survey and completing the questionnaire, participants were directed to click the submit option and the responded questionnaire was sent to google drive. Data retrieved from the online survey was entered into Microsoft Excel.

Sample size and study duration

The sampling was determined through the formula n (*minimum sample size*)=$z^2_{1-\alpha/2}$ $P(1-P)/d^2$. Where, $z^2_{1-\alpha/2}$= value of the standard normal variant for 95% CI and p=0.5 (anticipated population proportion) and d=0.6 (absolute precession on either side of the population proportion). The minimum sample size was computed as 266. However, the archived sample size was 300. The study duration was 15 days.

Study population

Health care workers in different hospitals in Odisha, India were permitted to be associated with this research. Demographic data analysed in the study population were age, gender, location, job category, working environment, and experience in years.

Questionnaire and data collection

A pilot study was done on 20 HCWs to validate the questionnaire. The pilot study data were excluded from the main analysis. The questions were organized in google forms, link was generated and shared with the participants. The link was also shared personally with HCWs who are on the contact list of the investigators. On clicking the link, the first page contains the study objectives, procedure, confidentiality agreement, voluntary participation, and consent to participate in the study. Identification information of the participants was not recorded anywhere in the questionnaire. Participants could withdraw from the study if they so desired at any point of time. Missing data was minimized by requesting the participants to answer all the questions in a section before proceeding to the next section. The participant's consent to participate in the study by clicking on the next button which takes them to the questionnaire on demographic characteristics. The participant has to answer all the questions in each section to proceed to the next section. Finally, the participant has to click on the submit button to submission of the form to google drive. The Snowball sampling method was followed.

Instruments

The online survey using the DASS-21 questionnaire is frequently used to assess depression, anxiety, and stress. A score of 0 to 3 in the past 1 week was analysed for each participant. The final score is multiplied by two to obtain the cumulative score. Each of the three sub-scales: (DASS21-D), Anxiety (DASS21-A), and Stress (DASS21-S) has seven items. Each item comprises a statement and four short response options to reflect the severity and scored from 0 (Did not apply to me at all) to 3 (Applied to me very much, or most of the time). To yield equivalent scores to the full DASS 42, the total score of each scale is multiplied by two[5] and ranges from 0 to 42.[19]

Data processing and statistical analysis were undertaken by using IBM SPSS Statistics version 24.0. The severity of DAS was classified according to normal, mild, moderate, severe, and very severe based on the score given in the result tables. Descriptive statistics procedure, non-parametric Chi-square test, and Binomial test were used for the analysis of categorical variables. Kruskal Wallis test & Mann-Whitney test was performed for comparing continuous variables. Cut-off value p<0.05 was considered to indicate statistical significance.

Ethical approval

The participants were assured that their responses to the online questionnaire would remain anonymous. The research was approved by the Ethical Committee of IMS and SUM Hospital: Ref. No /DRI/ IMS.SH/SOA/2021/036.

Results

The sample respondents were predominantly young with 63.7% in the 21-30 years and 15.3% in the 31-40 years age group (p<0.001). The majority of respondents were females (61.7%) (p<0.001) and the urban area had more than the 4/5th share in the sample (83%). Among the respondents, the maximum of nearly 2/5th were doctors (40.3%), 1/3rd of nurses (35%), 1/6th of dentists (17.7%), and 7% of pharmacists (p<0.001). The majority were working in non-government sectors (81.7%) (p<0.001). The majority were having 1-5 years (59%) of experience (p<0.001). None were taking medication for depression, anxiety, and stress. About 9% and 7.3% were taking medication for diabetes and hypertension respectively (Table 1).

Table 1 Participants' socio-demographic characteristics (n=300).

Variable	Classification	No.	%	*p* value
Age in years	21-30	191	63.7	*p*<0.001*
	31-40	46	15.3	
	41-50	32	10.7	
	> 50	31	10.3	
Gender	Female	185	61.7	*p*<0.001#
	Male	115	38.3	
Location	Rural	51	17	*p*<0.001#
	Urban	249	83	
Job Category	Doctors	121	40.3	χ^2=85.547 *p*<0.001*
	Dentist	53	17.7	
	Nurses	105	35	
	Pharmacist	21	7	
Working	Govt.	55	18.3	*p*<0.001#
	Non Govt.	245	81.7	
Experience (years)	1-5	177	59	χ^2=93.140 *p*<0.001*
	6-10	47	15.7	
	>10	76	25.3	
Are you taking medications for anxiety/stress?	Yes	0	0	
	No	300	100	
Are you taking medications for depression?	Yes	0	0	
	No	300	100	
Are you taking medications for diabetes?	Yes	27	9	
	No	273	91	
Are you taking medications for hypertension?	Yes	22	7.3	
	No	278	92.7	

***Note**: #binomial p value, *non-parametric Chi-square p value, Govt: government.*

Overall, 42.7% of the health care workers were having depression (depression score ≥10). About 1/5th were having mild (18.4%), with scores (of 10-13), and moderate (19.3%), with scores of 14-20, a form of depression. Only 5% had a severe or very severe form of depression with a score ≥21. More than half (53.7%) of the health care providers were having anxiety (anxiety score ≥8). Nearly 1/10th was mild (12.3%), with scores 8-9, and 28.3% moderate, with scores 10-14, a form of anxiety. Little more than 1/10th had severe or very severe (13.3%), a form of anxiety with a score ≥15. In comparison to depression and anxiety, a relatively less proportion was under stress with a prevalence of 13.3% with a stress score of ≥15 (Table 2).

The depression score has a mean±SD of 8.7±6.8 and median (1st quartile Q1-3rd quartile: Q3) 8 (4-12). The mean±SD of the anxiety score was 8.8± 6.6 and the median (Q1-Q3) was 8 (4-12). Similarly, the mean±SD of the stress score was 9.4±5.8, and the median (Q1-Q3) was 8 (4-12). The mean±SD and median (Q1-Q3) of the total DAS score were 26.9±16.2 and 24 (18-34) respectively. The individual and overall DAS scores did not have a significant association with age, experience, location, and working place (p>0.05). The professional category has a significant association with depression, anxiety, stress, and overall DAS score (p<0.01). Doctors have the highest level of depression, anxiety, stress, and DAS score. Nurses followed by the dentist came next in order. Pharmacists were the least affected. Gender also played a significant association with anxiety and stress and overall DAS score. Females have a significantly higher level of anxiety and stress (p<0.05) (Table 3).

Table 4 presents a comparison of mean±SD, median (Q1-Q3) of depression, anxiety, and stress with medication. Health caregivers who are taking medication for diabetes did not have a significant association with depression, anxiety, stress and overall DASS. Medication taken for hypertension did not have a significant association with depression, stress and overall DASS (p>0.05) but have a significantly higher anxiety level with median (IQR) 10 (7.5-14) with p=0.039.

Table 2 Table 2 DASS 21 subscale severity ratings.

Depression	No.	%
Normal (0-9)	172	57.3
Mild (10-13)	55	18.4
Moderate (14-20)	58	19.3
Severe & very severe (21+)	15	5
Anxiety		
Normal (0-7)	139	46.3
Mild (8-9)	37	12.3
Moderate (10-14)	84	28
Severe & very severe (15+)	40	13.3
Stress		
Normal (0-14)	260	86.7
Mild (15-18)	27	9
Moderate (19-25)	12	4
Severe & very severe (26+)	1	0.3
Total	300	100

Table 3 Comparison of depression, anxiety, and stress scores with Socio-demographic variables.

Age group	N	Depression		Anxiety		Stress		Total DAS	
		Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
21-30	191	8.7±7.5	6 (4-14)	8.8±6.9	8 (4-12)	9.4±6.1	10 (6-14)	26.8±17.7	22 (16-34)
31-40	46	9.5±6.5	10 (3.5-12.5)	9.0±6.3	9 (4-12)	10±5.3	10 (6-14)	28.5±14.7	27 (21.5-36.5)
41-50	32	8.2±4.6	8 (4-11.5)	7.3±4.4	8 (4-10)	9.4±5.3	10 (6-13.5)	24.8±11.5	24 (18-32)
>50	31	8.7±4.5	8 (4-14)	9.7±6.6	8 (6-12)	9.2±5.3	10 (6-12)	27.6±12.7	28 (18-36)
Kruskal Wallis Test *p* value			0.558		0.522		0.844		0.414
Job Category									
Doctors	121	9.7±4.9	10 (4-14)	9.4±6.2	8 (4-14)	10.1±6.0	10 (6-14)	29.3±13.8	30 (20-38)
Dentist	53	8.0±8.7	6 (0-12)	7.1±7.6	6 (2-10)	8.5±7.7	8 (2-14)	23.5±22.6	22 (6-33)
Nurses	105	8.7±7.8	6 (2-12)	9.5±6.6	8 (4-12)	9.9±4.2	7 (10-12)	28±15.1	22 (20-32)
Pharmacist	21	5.4±3.6	4 (2-9)	5.7±3.3	6 (3-8)	5.1±3.2	6 (2-8)	16.2±7.8	18 (8-23)
Kruskal Wallis Test *p* value			*p*<0.001		*p*<0.001		*p*<0.001		*p*<0.001
Experience (Years)									
1-5	177	8.9±7.5	6 (4-14)	8.5±6.8	6 (4-12)	9.4±6.1	10 (6-14)	26.8±17.6	22 (16-34)
6-10	47	9.4±6.9	8 (4-14)	10.4±7.0	8 (6-14)	10.3±5.5	10 (6-14)	30.1±16.2	30 (20-38)
>10	76	8.0±4.6	8 (4-12)	8.3±5.5	8 (4-12)	8.8±5.2	8 (6-12)	25.1±12.2	24 (18-32)
Kruskal Wallis Test '*p*' value			0.736		0.119		0.429		0.368
Gender									
Female	185	9.1±7.0	8 (4-14)	9.5±6.5	8 (4-12)	9.8±5.0	10 (6-14)	28.4±14.9	24 (20-36)
Male	115	8.0±6.5	8 (4-12)	7.6±6.6	6 (2-12)	8.7±6.9	8 (2-12)	24.5±17.9	20 (12-32)
Mann-Whitney U's *p* value			0.311		0.010		0.026		0.010
Location									
Rural	51	8.3±7.7	4 (2-12)	7.8±7.3	6 (4-12)	10.1±7.4	10 (4-14)	26.2±20.2	22 (16-34)
Urban	249	8.0±6.6	8 (4-12)	9.0±6.4	8 (4-12)	9.2±5.4	10 (6-12)	27.1±15.3	24 (18-35)
Mann-Whitney U's *p* value			0.315		0.065		0.584		0.255
Working									
Govt	55	8.5±4.8	8 (4-12)	8.0±6.8	6 (4-12)	9.5±6.0	10 (6-14)	26.1±14.6	24 (16-36)
Non-govt	245	8.8±7.2	8 (4-14)	8.9±6.5	8 (4-12)	9.4±5.8	10 (6-13)	27.1±16.6	24 (18-34)
Mann-Whitney U *p* value			0.489		0.240		0.899		0.857
Total	300	8.7±6.8	8 (4-12)	8.8±6.6	8 (4-12)	9.4±5.8	10 (6-14)	26.9±16.2	24 (18-34)

Table 4 Comparison of depression, anxiety, and stress score with medication taken.

Variables	N	Depression		Anxiety		Stress		Total DAS	
		Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
Are you taking medications for Diabetes?									
Yes	27	7.9±5.3	8 (4-10)	9.4±6.4	10 (4-14)	9.2±5.9	10 (4-12)	26.4±14.0	26 (18-36)
No	273	8.8±6.9	8 (4-14)	8.7±6.6	8 (4-12)	9.4±5.8	10 (6-14)	27.0±16.4	24 (17-34)
Mann-Whitney U's *p* value			0.704		0.437		0.988		0.804
Are you taking medications for Hypertension?									
Yes	22	8.9±5.2	9 (4-12)	11.3±6.5	10 (7.5-14)	11.3±5.0	10 (9.5-13)	31.5±3.4	29 (23.5-36)
No	278	8.7±6.9	8 (4-14)	8.6±6.5	8 (4-12)	9.2±5.8	10 (6-14)	26.5±16.4	23 (16-34)
Mann-Whitney U's p value			0.505		0.039		0.104		0.067

The classification of depression, anxiety, and stress into positive screening was done with a cut-off score of >13, >9, and >18 respectively. These cut off were decided considering moderate, severe & very severe categories of depression, anxiety and stress level. There was no significant association between the positive screening of depression, anxiety, and stress scores with age groups (p>0.05). The professional category had a significant association with the positive screening of depression, anxiety, and stress (p<0.05). Doctors had the highest proportion of positive screening for depression, anxiety, and stress i.e, 52.1%, 48.8%, and 20.7% respectively, followed by nurses for depression (40.0%) and anxiety (42.9%). Positive screening of dentists for depression (34%) and anxiety (30.2%) which is lower than that of a nurse. Pharmacists have the lowest proportion of positive screening (Table 5).

Table 5 Comparison of depression, anxiety, and stress scores with Socio-demographic variables.

Age in years	Screening of Depression		Screening for Anxiety		Screening for Stress	
	Negative (≤13)	Positive (>13)	Negative (≤9)	Positive (>9)	Negative (≤18)	Positive (>18)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
21-30	118 (61.8%)	73 (38.2%)	115 (60.2%)	76 (39.8%)	168 (88%)	23 (12%)
31-40	21 (45.7%)	25 (54.3%)	23 (50%)	23 (50%)	37 (80.4%)	9 (19.6%)
41-50	17 (53.1%)	15 (46.9%)	22 (68.8%)	10 (31.3%)	28 (87.5%)	4 (12.5%)
> 50	16 (51.6%)	15 (48.4%)	16 (51.6%)	15 (48.4%)	27 (87.1%)	4 (12.9%)
χ^2 (p)	4.756 (0.191)		3.590 (0.309)		1.846 (0.605)	
Job Category						
Doctors	58 (47.9%)	63 (52.1%)	62 (51.2%)	59 (48.8%)	96 (79.3%)	25 (20.7%)
Dentist	35 (66%)	18 (34%)	37 (69.8%)	16 (30.2%)	45 (84.9%)	8 (15.1%)
Nurses	63 (60%)	42 (40%)	60 (57.1%)	45 (42.9%)	98 (93.3%)	7 (6.7%)
Pharmacist	16 (76.2%)	5 (23.8%)	17 (81%)	4 (19%)	21 (100%)	0 (0%)
Total	172 (57.3%)	128 (42.7%)	176 (58.7%)	124 (41.3%)	260 (86.7%)	40 (13.3%)
χ^2 (p)	9.370 (0.025)		9.869 (0.020)		13.034 (0.005)	

Discussion

The COVID19 pandemic has been correlated with the psychological impact among HCWs who are dealing at the forefront. Depression, anxiety, and stress symptoms were manifested during the pandemic. In the study by Amal M. Qasem Surrati *et. al*, depression, anxiety, and stress (DAS) are 27.9%, 35.5%, and 72% in HCWs respectively, whereas in our study DAS is found to be 42.7%, 53.6%, 13.3% respectively. Hence in our study, we could find a higher percentage of depression and anxiety among healthcare workers, particularly doctors and nurses which could be due to long hours of work, high exposure to the virulent pathogen, and associated high mortality.[20]

Another recent study by Al Ateeq *et al.* (2020) reported depressive disorder (55.2%) and anxiety disorder 51.4% similar to our study.[21] Gupta A K *et al*. reported depression and anxiety at 8% and 37.3% respectively amongst the Nepalese health workforce.[22] In contrast to our study in which a higher percentage of HCWs reported having depression and anxiety. In the current study, overall health care workers were having depression scores≥10. About 1/5th were having mild (18.4%), with scores (of 10-13), and moderate (19.3%),

with scores of 14-20, forms of depression. Only 5% had a severe or very severe form of depression with a score ≥21. More than half (53.7%) of the health care providers were having anxiety (anxiety score ≥8). Nearly 1/10th HCWs have mild anxiety (12.3%), with scores of 8-9, and 28.3% moderate, with scores of 10-14, the form of anxiety. Little more than 1/10th had severe or very severe (13.3%), a form of anxiety with a score ≥15. In comparison to depression and anxiety, relatively fewer proportions were under stress with a prevalence of 13.3% with a stress score of ≥15.

The individual and overall, DAS score did not have a significant association with age, experience, location, and working place (p>0.05). The professional category has a significant association with depression, anxiety, stress, and overall, DAS score (p<0.01). Doctors have the highest level of depression, anxiety, stress, and DAS score. Nurses followed by dentists came next in order. Pharmacists have the least score. Gender also played a significant association with anxiety and stress and overall DAS score. Females have a significantly higher level of anxiety and stress (p< 0.05) which was similar to the study done by Preethi Selvaraj *et al*, but in the study by Chatterjee SS *et al*, female HCWs had less depression, stress, and anxiety.[23,14]

Eman Alnazly *et al*. reported depression at 40%, anxiety at 60%, and stress at 35%. Depressive, anxiety and stress scores were 21.30±10.86, 20.37±10.80, and 23.33±10.87 respectively.[24] Current study reported a similar percentage for depression and anxiety but lesser severity for stress. The depression score was 8.7±6.8 and median (1st quartile Q1-3rd quartile: Q3) 8 (4-12). The anxiety score was 8.8±6.6 and the median (Q1-Q3) was 8 (4-12). The stress score was 9.4±5.8 and the median (Q1-Q3) was 8 (4-12). The mean±SD and median (Q1-Q3) of the total DAS score were 26.9±16.2 and 24 (18-34) respectively. The individual and overall DAS scores did not have a significant association with age, experience, location, and working place (p>0.05). The professional category has a significant association with depression, anxiety, stress, and overall DAS score (p<0.01). Doctors have the highest level of depression, anxiety, stress, and DAS score. Nurses followed by the dentist came next in order. Pharmacists were the least affected. Gender also played a significant association with anxiety and stress and overall DAS score. Females have a significantly higher level of anxiety and stress, unlike that reported by Eman Alnazly *et al*, where males, married, aged 40 years and older, having more clinical experience were suffering from psychological distress.

Preethi Selvaraj *et al* study revealed median (IQR) of 5.0 (2.0-8.0) for depression,6.0 (2.0-10.0) for anxiety and 3.0(1.0-8.0) for stress in females.[23] Our study reported 8(4-14), 8(4-12), and 10(6-14) for depression, anxiety, and stress respectively. A Korean study revealed 27% of depression during the respiratory syndrome outbreak whereas in our study it was 42.7% during the COVID19 pandemic.[25] This emphasizes that the HCWs have experienced severe mental exhaustion during this time of uncertainty. Similar results were deciphered from studies in China.[26-29]

The present study reveals that HCWs who are taking medication for diabetes did not have a significant association with depression, anxiety, stress, and overall DASS. Medication taken for hypertension did not have a significant association with depression, stress, and overall DASS (p>0.05) but have a significantly higher anxiety level with a median (IQR) 10(7.5-14) with p=0.039. whereas Chaterjee S S *et al* study showed that 5.9% of HCWs had major comorbidities like diabetes, hypertension, and COPD.[16]

Therefore, we can de-escalate the associated stress and anxiety by screening and providing tailor-made psychological support.[30]

Conclusion

High levels of depression, stress, and anxiety were observed in our study. Over half of HCWs had significant depression, and anxiety, and less than 30% had stress regardless of age. This was especially more pronounced in females for both stress as well as anxiety. A structured guideline on pandemic management may reduce the cognitive dissonance among HCWs and their overall psychological well-being.

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Conflicts of interest

There is no conflict of interest.

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Author Contributions

All the authors contributed to the conduct of the study. The conceptualization of the study was done by MB, DM, and DM, and MB contributed to the methodology of the study.SM, TM, and SP were responsible for the statistical analysis. DM, MB, TM, SM, SP, and SSM contributed to the manuscript review and editing.

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A cross-sectional study on the effect of bedtime smartphone usage on sleep quality, sleep duration and daytime sleepiness in medical students

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ABSTRACT

Background: Sleep is a physiological phenomenon. It is a condition of unawareness that the body regulates homeostatic. Sleep is essential because it plays a leading role in mental and physical function, removing toxins, preventing diseases, etc. Reduced sleep among young adults is becoming a significant health problem worldwide. Several factors have been shown to lead to poor sleep quality, but the reason smartphone use creates sleep disorders in young adults has attracted great curiosity for a few years. The study aimed to assess sleep quality, duration, and daytime sleep dysfunction among medical students who use their smartphones at bedtime.

Materials and methods: This cross-sectional study included 109 medical students. The data was collected using a pre-validated questionnaire about bedtime mobile phone usage and Pittsburgh sleep quality index (PSQI). The means were calculated, and the association was determined using statistical analysis.

Results: In the study, 60% of participants indicated poor sleep quality was due to prolonged bedtime smartphone usage. The average global PSQI score was 5.4±2.5.

Conclusion: This study concluded that participants had poor sleep quality measured by PSQI. In addition, prolonged smartphone usage during bedtime was strongly co-related to poor sleep latency.

Introduction

All human beings need good sleep for good health.[1] Sleep is a state of reversible consciousness where the body and mind are renewed, repaired, and evolved. One of the main cornerstones of adolescent development is good sleep.[2] Electronic gadgets have an undesirable influence on the sleep quality of most children and young adults.[3] Due to the revolution in the technology field, most phone users currently possess smartphones that can be used for accessing the internet online, chatting on social networks, playing games, and watching videos.[4] Hence in the modern age, the use of smartphones has increased exponentially, especially among young students. The usage of smartphones has become a method of relieving academic stress and mental pressure.[5] Late-night smartphone usage has become a norm among undergraduate students, leading to interrupted sleep and daytime sleepiness. Studies have revealed that sleep disturbances are hazardous for physical and mental problems, mainly during adolescence.[6] The decrease in sleep quality is not only associated with health problems but also leads to the poor academic performance of students.[7] Sleep deprivation among students isn't a new phenomenon. However, it has drawn more clinical and educational interest in the past few years. Many types of research have shown that impaired sleep quality is highly prevalent among medical students compared to students at other universities, which may be inferable to the vast academic load, several hours of clinical

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duties, and lifestyle choices. However, little research has been attempted to detect the presence of any correlation between the usage of smartphones at bedtime and the sleep quality of medical students. Hence this study aimed to study the existing research gap and establish the effect of late-night smartphone use on sleep quality, duration, and daytime sleepiness among medical students

Materials and methods

This cross-sectional study was conducted taking a batch of MBBS students consisting of 150 students from the 3rd year after obtaining the approval of the Institutional Ethical Committee (IEC).

Data collection

Data were collected by convenience sampling technique. All the students were invited to participate in the study. One hundred and nine out of 150 students completed the questionnaire, and the response rate was 72.6%. Informed consent was received from all volunteering participants. No pressure was exerted on the participants. Confidentiality was reassured and maintained. All the data were collected via a questionnaire. The data collected was analysed using SPSS 20. The quantitative variables were reported using the mean and the SD, whereas qualitative variables were reported as frequencies and percentages. Pearson's Chi-Square test was used to determine the associations between the qualitative variables. Group means were compared using ANOVA and t-tests wherever applicable. A *p*-value less than 0.05 was taken to be statistically significant.

Study tools

After obtaining the appropriate informed consent from the participants, an online questionnaire was generated using Google form and distributed to the participants via a WhatsApp group text. This online questionnaire was designed by the authors based on relevant required information extracted from a few previous studies.[8-11] All participants were given ample time to complete the questionnaire and also were allowed to complete it at their homes.

The questionnaire consisted of 4 main sections

1. Purpose of study and reassurance of maintaining the confidentiality
2. Demographic details
3. Smartphone usage
4. Pittsburgh sleep quality index (PSQI)

Pittsburgh sleep quality index (PSQI)

A standardised measure of sleep quality is PSQI.[12] There are 18 questions in the PSQI which has seven rated components. 1) sleep quality, 2) sleep latency, 3) habitual sleep efficiency, 4) sleep duration, 5) use of sleeping medication, 6) sleep disturbances, and 7) daytime dysfunction. Each question is allotted a score between 0 to 3. The scores of all the items are added together to obtain a final score that can range between 0 to 21. If the total score is more significant than equal to 5, it denotes poor sleep quality. If the score is below 5, it is considered good sleep quality.

Bedtime smartphone usage:

The smartphone is "a cell phone with additional software functions (as email or Internet browser)", and bedtime has been defined as "the time at which you usually get into your bed to sleep".[13,14] All participants were subjected to 5 questions. The first question was whether they use smartphones or not, the second question asked was, did they use them at bedtime and the third question put to them was, how frequently did they use the smartphone during bedtime: one to three times per month, once per week, several times per week, or every day. The fourth question asked to them was the purpose they used it for, such as internet surfing, calling, social networking, text messaging, video games, or watching videos like series, shows, movies, etc. The fifth question put to them was on the amount of time they spent using a smartphone at bedtime, and on the same basis, they were divided into five groups: less than 15 minutes, 15-30 minutes, 30-45 minutes, 45-60 minutes, and more than 60 minutes. During the analysis, for simplicity purposes, the study population was divided into three groups: group A: less than 30 minutes, group B: 30-60 minutes, and group C: more than 60 minutes

Results

Our study obtained results from 109 participants from a batch of 150 medical students. The average age of the study group was 22.14±1.03 years. The age of the participants was between 20 years to 26 years. It was found that more females (57.8%) participated in this study than males (42.2%) (Figure 1). Pittsburg sleep quality index was calculated for everyone by adding the scores of all seven components. The average global score was 5.4±2.5. The minimum score received was one, and the maximum score attained was 14. Table 1 indicates that the average PSQI score for both genders, the males had a score of 5.43±2.4, while the females had a score of 5.38±2.5, their association remained insignificant (*p*-value: 0.912). Forty individuals reported surfing the web before sleeping, thirty participants reported listening to podcasts, music, or audiobooks, twenty-eight reported texting before sleep, and twelve used their smartphones before sleeping. Ten reported playing video games before going to bed (Figure 2). Number of individuals having good sleep quality (i.e., PSQI score <5) was 42 (38.5%), and those were having decreased sleep quality (i.e., PSQI score ≥5) was 67 (61.5%) (Figure 3). Table 2 depicts PSQI score and its association with its components we found out that there was a significant correlation between people having poor sleep quality and subjective sleep quality (p=0.002), sleep latency (p=0.000), sleep duration(p=0.000), habitual sleep efficiency (p=0.000), sleep disturbances (p=0.012), and daytime sleep dysfunction(p=0.001). However, we found out from our study that poor sleep quality was not related to the use of sleep medication (p=0.35). Table 3 shows the association between components of PSQI and duration of smartphone usage at bedtime; it was seen that only sleep latency was associated with increased duration of smartphone usage at bedtime (p=0.000). All the other components of PSQI compared with duration of smartphone usage at bedtime was found not to have any relationship, subjective sleep

quality (p=0.486), sleep duration (p=0.614), habitual sleep efficiency (p=0.51), sleep disturbances(p=0.332), using of sleep medication (p=0.754), and daytime dysfunction (p=0.981). It was found that the maximum number is sixty-four of them watching videos and browsing social media.

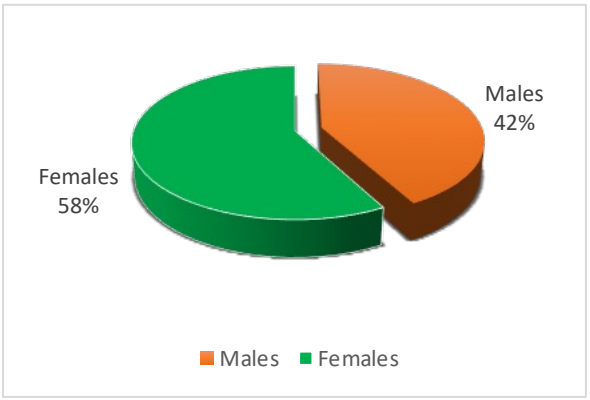

Figure 1 *Gender distribution of the participants.*

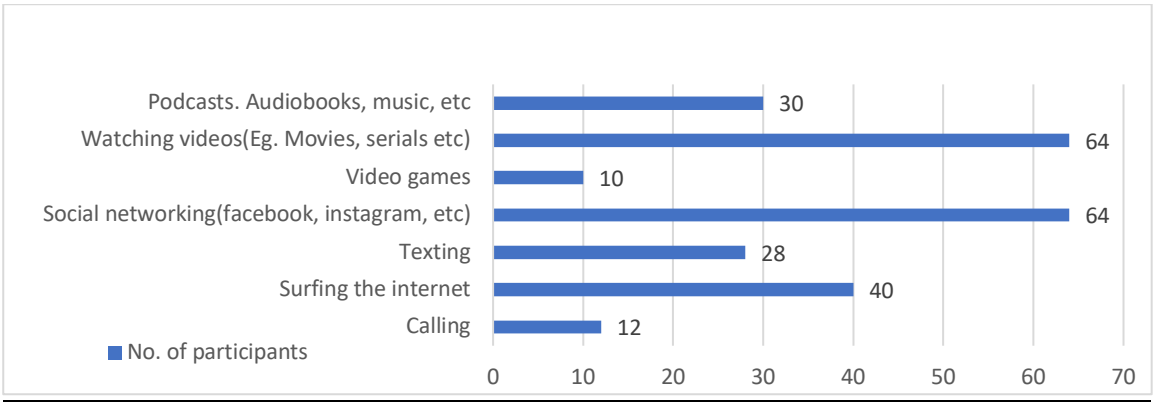

Figure 2 *Distribution of participants based on different usage of smartphones at bedtime.*

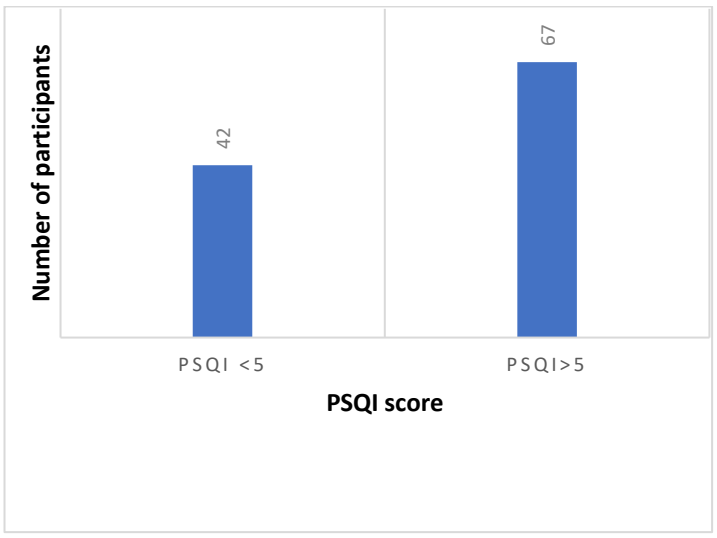

Figure 3 *Distribution of participants into good and poor sleep quality based on PSQI Score.*

Table 1 PSQI Global score as per gender.

Gender	PSQI Global Score	*p**
Males	5.43±2.5	0.912
Females	5.38±2.5	

***Note**: *p<0.05 is considered significant using an independent T-test.*

Table 2 Association between global PSQI scores and the components of PSQI.

Components of PSQI	Classification	PSQI Score		*p*
		<5	≥5	
Subjective sleep quality	Very good	17	8	0.002*
	Fairly good	24	53	
	Fairly bad	1	6	
	Very bad	0	0	
Sleep latency	No problem at all	15	8	0.000*
	Only a very slight problem	24	29	
	Somewhat of a problem	2	22	
	A very big problem	1	8	
Sleep duration	No problem at all	26	11	0.000*
	Only a very slight problem	11	22	
	Somewhat of a problem	5	24	
	A very big problem	0	10	
Habitual sleep efficiency	No problem at all	42	42	0.000*
	Only a very slight problem	0	15	
	Somewhat of a problem	0	8	
	A very big problem	0	2	
Sleep disturbances	No problem at all	7	9	0.012*
	Only a very slight problem	35	43	
	Somewhat of a problem	0	13	
	A very big problem	0	2	
Use of sleep medication	No problem at all	42	62	0.35
	Only a very slight problem	0	1	
	Somewhat of a problem	0	2	
	A very big problem	0	2	
Daytime dysfunction	No problem at all	26	22	0.001*
	Only a very slight problem	16	28	
	Somewhat of a problem	0	14	
	A very big problem	0	3	

***Note**: p<0.05 is considered significant, * significant value set at 0.05 using chi-square test.*

Table 3 Association between components of PSQI and duration of smartphone usage before sleep (n=109).

Bedtime smartphone usage		Group A	Group B	Group C	*p**
PSQI Components					
Subjective sleep quality	Very good	13	9	2	0.486
	Fairly Good	39	29	3	
	Fairly bad	2	5	9	
	Very bad	0	0	0	
	Total	52	38	14	
Sleep latency	<15 min	15	5	3	0.000*
	15-30 min	33	15	5	
	31-60 min	4	19	1	
	>60 min	2	4	3	
	Total	54	43	12	
Sleep duration	>7 hr	15	16	6	0.614
	6-7 hr	19	12	2	
	5-6 hr	16	11	2	
	<5 hr	4	4	2	
	Total	54	43	12	
Habitual sleep efficiency	>85%	44	29	11	0.51
	74-84%	6	9	0	
	65-74%	3	4	1	
	<65%	1	1	0	
	Total	54	43	12	
Sleep disturbances	No problem at all	10	5	1	0.332
	Only a very slight problem	37	31	10	
	Somewhat of a problem	7	6	0	
	A very big problem	0	1	1	
	Total	54	43	12	
Use of sleep medication	No problem at all	50	42	12	0.754
	Only a very slight problem	1	0	0	
	Somewhat of a problem	1	1	0	
	A very big problem	2	0	0	
	Total	54	43	12	
Daytime dysfunction	No problem at all	23	20	5	0.981
	Only a very slight problem	23	16	5	
	Somewhat of a problem	6	6	2	
	A very big problem	2	1	0	
	Total	54	43	12	

***Note**: *Significant value set at 0.05 using chi-square test.*

Discussion

Our study found that all medical students owned a smartphone, and nearly 98 (90%) of them use their smartphones at bedtime for various activities. Of the 98 participants who used their smartphones at bedtime, 60 (61.2%) had poor sleep quality. The sleep quality of all the participants was determined using the PSQI questionnaire, from which we found that 67 (61.5%) had poor sleep quality. We found that there was no significant relationship between quality of sleep and gender. Our finding was consistent with a Moroccan study which revealed that there were no gender differences between male and female medical students concerning poor quality of sleep.[15] Fobian et al. told that using media at bedtime and remaining awakened by the use of smartphone were related to lowering of the efficiency of sleep in adolescents.[16] Lemola *et al*. found a correlation between using electronic media during the night and sleep disturbance and concluded it to be a potential mediator for depressive symptoms.[17] Similar cross-sectional study taking 3,139 adolescents from America revealed that smartphone use at bedtime was related to sleeplessness and daytime sleepiness.[18] Our study confirmed that the prolonged usage of smartphones at bedtime was associated with poor sleep quality, daytime dysfunction, and prolonged sleep latency. Further research must be done to ascertain the causal relationship between poor sleep quality and smartphone usage. Few recently conducted studies have concluded that mobile phone screens emitted blue light, which is the main factor responsible for the poor sleep quality in people using mobile phones late at night. Mostly the screens of mobile phone release blue light of wavelengths ranging from 400-495 nm, which is capable of causing a phase-shifting in the circadian rhythm of humans or hampering the biological clock by reducing melatonin production.[19,20] Decrease in melatonin levels has further been responsible for increased sleep latency and disturbances.[21] Further, prolonged exposure to blue light enhances the alertness of our brain, and the cognitive functions are stimulated, resulting in poor sleep quality.[22, 23] The findings of our study also supported the facts mentioned above. As per our observation, the participants who used their smartphones for 30 minutes or more after getting into bed had prolonged sleep latency, reduced sleep duration, and daytime dysfunction. Additionally, the effects of blue light on the mobile phone screen while using the mobile phone before bedtime for searching the web, playing video games, watching Facebook for a prolonged period, or reading a negative email, may also lead to hyperexcitability both physical and mental, contributing to hyperarousal condition and poor sleep quality.[24,25] Some studies have indicated that putting a smartphone near or under the pillow during sleep can cause prolonged latency of sleep, sleep disturbances, and daytime sleep dysfunction. The factors that contribute to these effects may be attributed to an irresistible desire to go through notifications received and the updates being displayed on the mobile phone, disturbances that are produced by the vibrating phone while receiving new notifications and recent messages, the heat produced by charging phones, and RF-EMF (radiofrequency and electromagnetic fields) exposure from the smartphone.[25] The reasons mentioned above are suspected to be the underlying cause of sleep problems like excessive daytime sleepiness, sleep disturbances, and increased sleep latency, observed in our study participants. Our study confirmed that prolonged usage of smartphones at bedtime was strongly associated with poor sleep quality, daytime dysfunction, and prolonged sleep latency. Further research must be done to ascertain the causal relationship between poor sleep quality and smartphone usage.

Conclusion

From this study, we conclude the following points. We observed a significant association between prolonged (>60 minutes) bedtime smartphone usage and the sleep latency component of the PSQI (*p*-value=0). Most medical students (61.5%) had poor sleep quality (i.e. PSQI score ≥5). Lastly, there was no significant relationship between sleep duration and daytime sleepiness, but there was a significant correlation between poor sleep quality and all the components of PSQI. Therefore, the main implication of this study is that, through this study, the authors urge young adults to restrict the use of smartphones during bedtime, thereby preventing subsequent health hazards.

The limitations of this study were the short duration of two months and a smaller number of participants consisting of MBBS students of a single batch. Further research can be done by taking a more significant number of participants in multicentred studies to assess the sleep quality among medical students.

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Conflicts of interest

Nil.

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Psychometric properties of a new occupational therapy cognitive outcome measure for Thai older adults with cognitive impairments

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ABSTRACT

Background: Occupational therapy (OT) cognitive interventions requires a standardised cognitive outcome measure to help explain the effectiveness of the interventions. Now, there is a lack of measures to use for Thai older adults with cognitive impairments. Therefore, a new Occupational Therapy Cognitive Outcome Measure (OTCOM) for Thai older adults with cognitive impairments was developed to support evidence-based OT cognitive interventions.

Objectives: To examine the psychometric properties including internal consistency, inter-rater and intra-rater reliability, known-group construct validity, concurrent validity, and responsiveness of the OTCOM.

Materials and methods: A prospective cohort design was used in this study. One hundred and ten older adults; sixty-one older adults with cognitive impairments and forty-nine older adults without cognitive impairments, were recruited. The Cronbach's alpha coefficient was calculated for internal consistency. Intraclass correlation coefficient (ICC) was used to analyse rater reliability. Analyses of concurrent and known-group construct validity were done using Pearson correlation and independent t-test, respectively. Both effect size (ES) and standardised response mean (SRM) were calculated for responsiveness of the OTCOM.

Results: The results showed good internal consistency (α=0.88), and excellent inter-rater and intra-rater reliability (ICC=0.99). A high correlation between the OTCOM and the Dynamic Lowenstein Occupational Therapy Cognitive Assessment-Geriatric (DLOTCA-G) and the Thai Cognitive-Perceptual Test (Thai-CPT) was found, indicating good concurrent validity. There was a significant difference between older adults with cognitive impairments and without cognitive impairments, suggesting good construct validity by the known-group method. Responsiveness was shown as large ES and SRM in the total score.

Conclusion: The OTCOM showed good psychometric properties, making it useful in OT practice after revisions.

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Introduction

Due to increasing life expectancies, many countries have experienced an unprecedented and continued growth of senior citizens. In 2020, over 700 million persons worldwide were older adults aged 65 years and over.[1] In the same year, Thailand had over 17% of its population comprised of older adults, making it an aged society.[2] This growth is an essential transformation in the 21st century that affects society, family structure, financial market, and health goods and services. According to the 2030 Agenda for Sustainable Development of the United Nations, all segments of society, including older adults, cannot be left behind. Governments worldwide must address concerns about older adults' health and well-being.[1] A typical age-related health problem in older adults is cognitive impairments (CI) that can develop into dementia.[3] CI can affect the quality of life of older people due to a loss of functional ability, and the need to maintain their sense of independence.[4,5] Occupational therapists (OTs) have a role in maintaining the quality of life of older adults.[6] For evidence-based practice, the quality of occupational therapy (OT) service in cognition for clients with CI should be explained through standardised cognitive outcome measures.[7] Outcome measure explain the effectiveness of the overall intervention. Therapists can compare different interventions using the appropriate outcome measure during interventions and choose the best intervention. An appropriate outcome measure may help determine a suitable intervention plan.[8] There are currently fewer evidence-based cognitive interventions for clients with CI compared to other common diseases. Inappropriate or poorly chosen outcome measures may weaken or invalidate the result's interpretation.[9] Therefore, good psychometric properties regarding reliability, validity, and responsiveness based on careful research should be considered.[7,10] Since there is a lack of standardised OT cognitive outcome measures appropriate for older adults with CI in Thailand, Thai occupational therapists typically use cognitive screening tests such as the Thai Mental State Examination or assessment tools developed for neurological patients such as the Thai Cognitive-Perceptual Test. These tests might not sensitive enough to detect cognitive change over time.[11] This might bring confusion in interpreting the effectiveness of treatment.[8] Therefore, a reliable, valid, sensitive, and context-suitable outcome measure for evaluating cognitive function in Thai older adults is needed.

In this study, an outcome measure to assess cognitive functions of Thai older adults aged sixty years and over who had CI has been developed by the researchers. This outcome measure is named the Occupational Therapy Cognitive Outcome Measure (OTCOM). The OTCOM employs both subjective and objective approaches. The subjective method is necessary to understand the client's perception and expected standard. It is based on personal feelings. The subjective measure is often obtained through questionnaires having degrees of agreement; consequently, it may be interpreted as a quantitative score. The objective approach is based on an individual's performance. Its strength is that the client's performance can be defined in quantitative terms. The value is that the score results can efficiently and reliably be compared with others.[12] Furthermore, the OTCOM employs a dynamic measurement approach. As a dynamic measure, therapists can learn what components can be extended and which strategies can encourage each client[13,14] because the dynamic measures focus on the degree of change resulting from introducing the mediation during assessment.[15] It is believed that therapists could observe the client's responses while receiving mediation and gain information about the processing strategies of the clients. As a result, the dynamic measure can help the therapist create a suitable intervention program.[13,14]

This study aimed to examine the psychometric properties of the OTCOM when used in Thai older adults with CI so that it can be used to support evidence-based OT interventions

Materials and methods

Participants. One hundred and ten older adults aged sixty years and older were recruited with purposive sampling from five settings: communities in Chiang Mai, Chiangmai Neurological Hospital, Queen Savang Vadhana Memorial Hospital in Chonburi, Geriatric Medical Center in Chiang Mai, and Ishii Stroke Rehabilitation Center in Bangkok. Sixty-one of the older adults had cognitive impairments (CI) and there were forty-nine older adults without CI (Non-CI). The inclusion criteria of the CI group were: 1) had a CI as initially screened by a physician or psychiatrist 2) received a score of 10-24 as determined by the Montreal Cognitive Assessment (MoCA) or the Montreal Cognitive Assessment Basic (MoCA-B) (Copyright Z. Nasreddine MD. Reproduced with permission) 3) Self-identified as now requiring minimal assistance for ADLs and being independent previously and 4) no depression as assessed by the Thai Geriatric Depression Scale-15 (TGDS-15). Inclusion criteria of the Non-CI group included: 1) never had diagnosis of a CI and 2) received a score of 25-30 on the MoCA or the MoCA-B.

Instrumentation. Instruments were categorized into three groups.

Screening instruments. Cognitive screen tools and depression screen tools were used. The cognitive screening tools for mild cognitive impairments are the Montreal Cognitive Assessment (MoCA) Thai version, 2011 and the Montreal Cognitive Assessment Basic (MoCA-B) Thai version, 2014. They have 81-99% rating for sensitivity and specificity.[16] The MoCA was used when the participant's education was 5 years or more and the MoCA-B was used if their education was less than 5 years. The short screening tool used for detecting depression in older adults was the Thai Geriatric Depression Scale-15 (TGDS-15). It has a sensitivity of 0.92 and a specificity of 0.87.[17]

Research instruments. Three instruments were used; the Dynamic Lowenstein Occupational Therapy Cognitive Assessment-Geriatric (DLOTCA-G), the Thai Cognitive-Perceptual Test (Thai-CPT), and the cognitive training program. The DLOTCA-G has excellent inter-rater reliability (r=0.98), and internal consistency at α=0.26-0.85.[18] In this study, five subtests of the DLOTCA-G, Orientation of Time, Orientation

of Place, Copy Geometric Forms, Motor Imitation, and Pictorial Sequence A, were used to study for a relationship with the OTCOM. The Thai-CPT is a perceptual-cognitive outcome measure for patients with brain injuries in Thailand. It has acceptable internal consistency (α=0.78-0.96), good to excellent test-retest reliability (ICC=0.83-0.97), and excellent inter-rater reliability (ICC=0.91-1.00).[19] Four subtests of the Thai-CPT, Auditory Object Name Memory, Object Recognition, Categorization, and Problem Solving, were used in this study. Finally, the cognitive training program described in the study of Munkhetvit, Rattakorn, Apikomonkorn and Punyanon[20] was used. This efficacious intervention includes 15 sessions, with three sessions a week for 60 minutes each.

The Occupational Therapy Cognitive Outcome Measure (OTCOM) was developed by the researchers based on information processing theory,[21] the Toglia's Dynamic Interactional Approach,[22] the Cognitive Disabilities Reconsidered Model,[23] DSM-5,[24] relative cognitive assessment tools, and the researchers' clinical experience. The measure contains two parts: the self-report section and the performance-based measure. The self-report section is a subjective questionnaire containing 26 subtests. The performance-based section is a bottom-up objective cognitive measure with a dynamic prompt. The performance-based section includes 24 subtests in seven cognitive domains: Orientation, Attention, Memory, Perceptual-Motor Function, Language, Executive Functions, and Social Cognition, as a static measure. Out of seven domains, five domains and 15 subtests are dynamic measures (Table 1). The performance-based section has an acceptable content validity (IOC=0.67-1.00) as determined by three experts: a psychiatrist who has experience in cognitive intervention, and more than five years of assessing the psychometric properties of cognitive tests; an occupational therapy lecturer who has experience in cognitive assessments and interventions, and more than five years of experience teaching about cognitive impairments in the elderly; and an occupational therapist who has more than five years of experience in cognitive interventions and assessments for the elderly with CI. In this study, the self-report section and seven domains in the performance-based section were studied for their psychometric properties.

Table 1 Structure of the Occupational Therapy Cognitive Outcome Measure (OTCOM).

Self-report section:	**26 subtests questionnaire**		
Performance-based section:	**Domain**	**Subtest**	**Mediation**
	Orientation	Orientation of Time	-
		Orientation of Place	-
	Attention	Selective Attention A	3 level
		Selective Attention B	3 level
		Processing Speed	-
	Memory	Immediate Recall Memory	-
		Recognition Memory	-
		General Semantic Memory	2 level
		Delayed Recall Memory	2 level
	Perceptual-Motor Function	Geometric Copy	2 level
		Pantomime Praxis	2 level
		Imitation Praxis	4 level
		Using Object Praxis	3 level
	Language	Naming	-
		Semantic Fluency	-
		Receptive Language	-
	Executive Functions	Flexibility	4 level
		Abstract Thinking	2 level
		Categorization	4 level
		Sequencing A	4 level
		Sequencing B	4 level
		Problem Solving	2-3 level
	Social Cognition	Recognition of Emotions	2 level
		Theory of Mind	-
	Awareness	Awareness of Cognitive Decline	-
		Awareness of Memory	-

Procedures

To examine the psychometric properties of the OTCOM, a prospective cohort design was utilized. Ethical approval was obtained by the follow review boards: Ethics Committee at the Faculty of Associated Medical Sciences, Chiang Mai University (approval # AMSEC-61FB-001), the Research Ethics Committee No. 2, Faculty of Medicine, Chiang Mai University (approval # 6928), the Ethics Committee at Chiangmai Neurological Hospital (approval # 021-63), and the Institution Review Board at Queen Savang Vadhana Memorial Hospital (approval # 001/2564). All participants signed a consent form after verbal and written explanation of the study was provided.

One hundred and sixteen older adults were recruited with one hundred and ten older adults meeting the inclusion criteria. The participants were divided into two groups: the cognitive impairment (CI) group (61 older adults) and the Non-CI group (49 older adults).

Internal consistency. All participants in the CI group were assessed by the OTCOM. The data was calculated using Cronbach's alpha coefficient. A Cronbach's alpha coefficient lower than 0.50 was considered unacceptable, 0.50-0.59 is poor, 0.60-0.69 is questionable, 0.70-0.79 is acceptable, 0.80-0.89 is good, and 0.90-1.00 is excellent.[25]

Validity. Construct and concurrent validity were examined. For the known-group construct validity, all participants were assessed by the performance-based section of the OTCOM. The data of the two groups were compared using independent t-test. For concurrent validity, the CI group were assessed by three measures; the OTCOM, the DLOTCA-G, and the Thai-CPT. Fifty-seven older adults with CI completed the Thai-CPT and the DLOTCA-G, four older adults were unable to complete the assessments. The data from the three measures were analysed for correlation using the Pearson Correlation Coefficient. Correlation is poor at <0.40, modest at 0.40–0.74, and excellent at >0.75.[26]

Reliability. Rater reliability has two examination methods: inter-rater reliability and intra-rater reliability. Only the performance-based section of the OTCOM was used to examine for rater reliability. For inter-rater reliability, ten participants in the CI group were independently assessed by two assessors who are occupational therapists and passed intensive training in using the OTCOM by an author. Ten participants were chosen based on research following Washington and Moss.[37] The two sets of scoring were analysed by the intraclass correlation coefficient (ICC). For intra-rater reliability determination, ten participants were re-assessed 10-14 days later by the same assessor. The two sets of data were analysed using the ICC. The ICC values that were less than 0.50 indicated poor reliability; between 0.50 and 0.75 were moderate, between 0.75 and 0.90 was good, and greater than 0.90 is considered excellent.[27]

Responsiveness. To examine internal responsiveness, change in measure between pre- and post-intervention was considered.[28] After pre-intervention assessment by the performance-based section of the OTCOM was done, thirty-four out of sixty-one subjects in the CI group participated in the cognitive training program. Thirty-two subjects completed the program. Within a week of finishing the program, they received a re-assessment. The scores from pre-intervention and post-intervention were calculated by effect size (ES) and standard response mean (SRM). The ES can be calculated by dividing the mean of the difference between pre- and post-intervention by the standard deviation of pre-intervention. The SRM is the mean of difference between pre- and post-intervention divided by the standard deviation of change. When considering the ES and SRM, 0.20 is indicated as small, 0.50 is medium, and over 0.80 is large.[29,30]

Results

The average age of the CI group was 71±9 years, and the non-CI group was 66±4 years. Over 60% of both groups were female. A large proportion of both groups (67.30% for the non-CI group and 73.80% for the CI group) had a disease, such as hypertension disease. All participants in the non-CI group had at least one year of education. Both groups had many participants with more than nine years of education with CI Group at 49.30% and the non-CI group at 81.70%. Most participants in the CI group had a cognitive impairment with mild symptoms with MoCA score 18-24 (n=44, 72.13%).

Internal consistency was acceptable for the self-report section (α=0.72) and good for the performance-based section (α=0.86). The findings of known-group construct validity found that the CI group had a lower score from the OTCOM in every single subtest compared with the Non-CI group. The difference in scores of both groups was significant (p<0.05) except for the subtest Using Object Praxis and Imitation Praxis. Table 2 illustrates the difference of the subtest Imitation Praxis (t=1.964, p=0.052) that was more than the subtest Using Object Praxis (t=0.895, p=0.373). In Table 3, the correlation between the OTCOM and the Thai-CPT was a poor to modest correlation on the subtests; Auditory Object Name Memory, Object Recognition, Categorization and Problem Solving (r=0.36-0.56, p<0.01). The OTCOM and the DLOTCA-G showed excellent correlation in the subtest Orientation of Time (r=0.77, p<0.01) and a modest correlation in the subtest Orientation of Place and Sequencing A and B (r=0.39-0.62, p<0.01). A poor correlation was found in the subtest Geometric Copy (r=0.27, p=0.05). Only the subtest Imitation Praxis had no correlation (r=0.14). Table 4 shows excellent intra-rater and inter-rater reliability (ICC=0.99).

Table 2 Difference in the OTCOM score between the cognitive impairment (CI) and the without cognitive impairment (non-CI) group calculated by the t-test for independent subjects.

Domain	Subtest (maximum score)	Group	n	Mean±SD	*t*	Sig. (2-tailed)
Orientation	Orientation of Time (5)	CI	61	4.36±1.14	-3.686	0.000**
		Non-CI	49	4.92±0.28		
	Orientation of Place (4)	CI	61	3.72±0.61	-2.549	0.013*
		Non-CI	49	3.94±0.24		
Attention	Selective Attention A (8)	CI	61	7.69±0.99	-2.028	0.046*
		Non-CI	49	7.96±0.29		
	Selective Attention B (16)	CI	61	13.79±3.29	-3.172	0.002**
		Non-CI	49	15.37±1.87		
	Processing Speed (10)	CI	61	9.11±1.66	-3.389	0.001**
		Non-CI	49	9.90±0.51		
Memory	Immediate Recall Memory (6)	CI	61	4.62±1.08	-2.197	0.030*
		Non-CI	49	5.04±0.91		
	Recognition Memory (10)	CI	61	8.89±1.74	-3.524	0.001**
		Non-CI	49	9.73±0.64		
	General Semantic Memory (5)	CI	61	4.61±0.82	-3.233	0.002**
		Non-CI	49	4.96±0.20		
	Delayed Recall Memory (5)	CI	61	2.48±1.68	-2.893	0.005**
		Non-CI	49	3.33±1.40		
Perceptual-Motor Function	Geometric Copy (5)	CI	61	3.84±1.56	-4.545	0.000**
		Non-CI	49	4.82±0.56		
	Pantomime Praxis (10)	CI	61	9.54±0.69	-4.463	0.000**
		Non-CI	49	9.96±0.20		
	Imitation Praxis (10)	CI	61	9.39±1.05	-1.964	0.052
		Non-CI	49	9.71±0.64		
	Using Object Praxis (10)	CI	61	9.97±0.25	-0.895	0.373
		Non-CI	49	10.00±0.00		
Language	Naming (13)	CI	61	12.85±0.40	-2.299	0.024*
		Non-CI	49	12.98±0.14		
	Semantic Fluency (10)	CI	61	5.70±2.35	-3.486	0.001**
		Non-CI	49	7.20±2.09		
	Receptive Language (5)	CI	61	1.59±1.54	-4.699	0.000**
		Non-CI	49	2.92±1.38		
Executive Functions	Flexibility (12)	CI	61	8.15±3.90	-6.303	0.000**
		Non-CI	49	11.61±1.60		
	Abstract Thinking (5)	CI	61	3.61±1.68	-5.485	0.000**
		Non-CI	49	4.84±0.42		
	Categorization (5)	CI	61	3.98±1.47	-4.366	0.000**
		Non-CI	49	4.86±0.45		
	Sequencing A (5)	CI	61	4.16±1.33	-4.171	0.000**
		Non-CI	49	4.90±0.30		
	Sequencing B (5)	CI	61	4.31±0.94	-2.779	0.007**
		Non-CI	49	4.69±0.46		
	Problem Solving (12)	CI	61	10.51±1.76	-5.141	0.000**
		Non-CI	49	11.73±0.53		
Social Cognition	Recognition of Emotions (5)	CI	61	4.49±0.67	-2.431	0.017*
		Non-CI	49	4.78±0.55		
	Theory of Mind (5)	CI	61	4.92±0.27	-2.315	0.024*
		Non-CI	49	5.00±0.00		

** p<0.05, **p<0.01*

Table 3 Correlation between OTCOM and Thai-CPT and between OTCOM and DLOTCA-G was calculated by Pearson correlation (n=57).

Subtest	OTCOM vs. Thai-CPT			OTCOM vs. DLOTCA-G		
	OTCOM	Thai-CPT	*r*	OTCOM	DLOTCA-G	*r*
	mean±SD	mean±SD		mean±SD	mean±SD	
Orientation of Time				4.42±1.13	7.39±1.26	0.77**
Orientation of Place				3.77±0.54	7.72±0.94	0.62**
Immediate Recall Memory	4.63±1.03	5.26±1.09	0.50**			
Recognition Memory	9.02±1.59	9.35±1.67	0.36**			
Geometric Copy				3.88±1.51	4.75±0.64	0.27*
Imitation Praxis				9.42±1.03	6.67±1.34	0.14
Categorization	4.12±1.35	2.51±0.63	0.49**			
Sequencing A & B				8.70±1.79	4.35±1.17	0.39**
Problem Solving	10.67±1.47	13.68±1.65	0.56**			

*Note: OTCOM: Occupational Therapy Cognitive Outcome Measure, Thai-CPT: Thai Cognitive-Perceptual Test, DLOTCA-G: Dynamic Lowenstein Occupational Therapy Cognitive Assessment-Geriatric, *p<0.05, **p<0.01.*

Table 4 Rater reliability of the OTCOM calculated by intraclass correlation coefficient (ICC).

Domain	Inter-rater reliability			Intra-rater reliability		
	n	ICC	Interpretation	n	ICC	Interpretation
Total	10	0.99	excellent	10	0.99	excellent
Orientation	10	1.00	excellent	10	0.99	excellent
Attention	10	0.99	excellent	10	0.99	excellent
Memory	10	0.99	excellent	10	0.99	excellent
Perception-Motor Function	10	0.99	excellent	10	0.99	excellent
Language	10	0.99	excellent	10	0.99	excellent
Executive Function	10	0.99	excellent	10	0.99	excellent
Social Cognition	10	0.99	excellent	10	0.99	excellent

For responsiveness of the OTCOM, it was found that the thirty-two CI participants had positive change, and there was large effect of both ES (0.83) and SRM (1.42) in total score (Table 5). This was also the case in the Language domain (ES =0.89 and SRM=1.01) and Executive Functions domain (ES=0.90 and SRM=1.32). Three domains; Memory, Perception-Motor Function, and Social Cognition, had a medium effect at ES=0.50-0.66 and SRM=0.54-0.78.

Table 5 Effect size (ES) and standardized response mean (SRM) of responsiveness in CI group with mild and moderate symptoms.

Domain (Maximum Score)	n	Pre-intervention score	Post- intervention score	Change score	ES	SRM
		mean±SD	mean±SD	mean±SD		
Orientation (9)	32	8.06±1.46	8.53±1.05	0.47±0.95	0.32	0.49
Attention (34)	32	29.31±5.86	31.75±4.04	2.44±3.84	0.42	0.63
Memory (26)	32	20.94±3.52	23.25±2.98	2.31±3.03	0.66	0.76
Perceptual-Motor Function (35)	32	32.56±2.40	33.75±1.81	1.19±1.53	0.50	0.78
Language (28)	32	20.00±3.35	22.97±3.63	2.97±2.95	0.89	1.01
Executive Functions (44)	32	33.84±7.47	40.59±4.70	6.75±5.12	0.90	1.32
Social Cognition (10)	32	9.53±0.72	9.91±0.30	0.38±0.71	0.53	0.54
Total score	32	154.25±19.93	170.75±14.67	16.50±11.61	0.83	1.42

Discussion

The purpose of this study was to examine the psychometric properties of a new cognitive outcome measure for Thai older adults known as the Occupational Therapy Cognitive Outcome Measure (OTCOM). Internal consistency, known-group method of construct validity, concurrent validity, rater reliability, and responsiveness were all investigated.

Internal consistency. Cronbach's alpha coefficient of inter-item correlation of the OTCOM were between 0.72-0.86 which indicated an acceptable and good internal consistency.[25] High inter-item correlation shows that items of the test measure the same construct.[31] Hence, it can be noted that the items in the OTCOM measured the same attributes, that is cognitive function. This reflects that the constructs of the OTCOM were developed based on cognitive theories.[32]

Validity. For known-group construct validity, the significant difference between the CI group and Non-CI group was found in every subtest except Imitation Praxis (t=1.964, p=0.052) and Using Object Praxis (t=0.895, p=0.373). Examining the known-group validation demonstrates how the measure can differentiate members of one group from another group based on their scale scores. Its main concern is presenting evidence that the test measures what it claims to measure.[31] Based on significant differences found in this study it can be interpreted that the OTCOM can measure cognitive functions of older adults with CI. The reason why no significant difference was found in the subtest Imitation Praxis and Using Object Praxis might be due to a difference in the gestures used in the assessment. In the OTCOM, the participants were asked to imitate five transitive gestures and five intransitive gestures that were uncomplicated and are familiar to the participants in their daily lives. As a result of imitating familiar gestures, both CI and Non-CI older adults could perform them automatically rather than trying to imitate. In the same way, the reason that no significant difference in the subtest Using Object Praxis was found might be because large numbers of the CI group had mild symptoms. Furthermore, they had almost had no problem in using those familiar objects, as shown in Table 2. These results suggest that the two subtests need to be revised. For Concurrent validity, there is a method of criterion-related validity that is a determination of an association of the target test with some criterion or gold standard test. To find the association, scores from the target test and the gold standard test must be gathered in the same period of time.[33] In this study, the correlation between the OTCOM and the DLOTCA-G and the Thai-CPT was determined. It was found that four subtests of the OTCOM, Immediate Recall Memory, Recognition Memory, Categorization, and Problem Solving, had a significant correlation with the Thai-CPT (r=0.36-0.56, p<0.01). Similarly, a significant correlation between the OTCOM and the DLOTCA-G was found in three subtests (r=0.39-0.77, p<0.01). However, the subtest Geometric Copy of the OTCOM had poor correlation (r=0.27) with the subtest Copy Geometric Forms of the DLOTCA-G. The poor correlation might be due to the difference of the geometric form and the number of copying used in the two tests. In the DLOTCA-G, there are three geometric objects that are copied; a circle, a triangle, and a rhombus; all forms are two-dimensional shapes whereas the OTCOM employed a copying of a three-dimensional shape, a pyramid. Griffiths, Cook and Newcombe[34] described that a person with a brain injury will likely have problems in three dimensional shapes compared with two-dimensional shapes. Three-dimensional shapes require more visual perception, visuospatial ability, and visuo-constructional skills. Dridan[35] indicated in recent studies that three-dimensional shapes can be useful in the clinical examinations for clients with a cognitive impairment. Another finding of the correlation was that there was no significant correlation between the subtest Imitation Praxis of the OTCOM and the subtest Motor Imitation of the DLOTCA-G. The possible reason might be the same as previously mentioned concerning different types of gestures used in the two tests. The gestures used in the OTCOM are five transitive gestures that are nailing with a hammer, writing with a pen, drinking a glass, combing hair, and brushing teeth, and five meaningful uncomplicated intransitive gestures that are a Thai greeting (Sawasdee), waving a hand to say "Bye-bye!", clapping hands, a thumbs up (a "good job!" sign), and a beckoning hand gesture. While the gestures used in the DLOTCA-G are four meaningless complicated intransitive gestures; such as "place palm on the neck of the same side and then on the opposite shoulder".[18] The study of Lesourd, Osiurak, Baumard, Bartolo, Vanbellingen and Reynaud[36] reported that imitating the meaningless gestures involves more brain areas than meaningful gestures. It should be noted that the subtest Imitation in the two measures was designed to test the different skills of praxis.

Reliability. The OTCOM revealed an excellent inter-rater and intra-rater reliability (ICC=0.99-1.00). This might be attributed to the OTCOM's manual and training. There is a clear explanation about operating and scoring in the manual. Before assessing, the assessors underwent an intensive training by the researcher. In addition, re-assessment within 10-14 days did not change the participant's cognitive function.[37]

Responsiveness. Overall, the OTCOM showed a medium to large effects (ES=0.50-0.90, SRM=0.54-1.32) in all domains except Attention and Orientation. This indicated that the Memory, Perceptual-Motor Function, Language, Executive Functions, and Social Cognition domains of the OTCOM could detect subtle changes of cognitive function of the participants in this study. However, the Attention domain had a small to medium effect (ES=0.42, SRM=0.63). This might be because the subtest Selective Attention B and Processing Speed in the Attention domain require inhibitory control and flexibility to perform the task whereas the cognitive training program used in this study[20] had no specific training in inhibitory skills. A large progression in this skill might not be detected. In addition, one limitation of this study is that there is no confirmation whether the participants had an inhibitory deficiency. In further revisions, an inhibitory subtest should be added. The findings that the Orientation domain revealed only a small change is

similar to the study of Carrion, Folkvord, Anastasiadou and Aymerich,[38] which systematically reviewed many cognitive training programs specifically on orientation and found just a small improvement in orientation. However, after the cognitive training program had been completed, several participants in this study used a shorter time for answering the oriented questions of the OTCOM. Perhaps the scale used in the Orientation domain might need more explanation in further revisions. For instance, it should add more points for a shorter time in answering or re-scale by integrating the four orientation levels, including x1, x2, x3, and x4 in scoring.[39]

Due to the COVID-19 pandemic and the social distancing countermeasures, the older adults with cognitive impairments did not receive occupational therapy services as they are non-emergency clients. As a result, the small sample size is a limitation of this study. Consequently, the factor analysis could not be examined. In future research, a larger sample size should be used to allow factor analysis to be done and the inhibitory subtest should be developed. Furthermore, the Orientation domain, the Attention domain, and Perceptual-Motor Function domain should be revised.

Conclusion

The OTCOM showed good reliability, validity, and responsiveness. It might be applied to assess cognition in older adults with cognitive impairment after revisions have been made.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Data Availability

The data are not publicly available. Please request the corresponding author at pachpilai.c@cmu.ac.th for information on access to data.

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Age and gender demographic and statistical analysis in oral squamous cell carcinoma in Eastern India

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) continues to dominate all the oral cancer cases with premalignant disorders, which can also be predictable at the pre-clinical phase of malignancy. Chewing behaviors such as betel quid, areca nut& tobacco are all major risk factors. The majority of OSCC patients present with advanced disease and a poor prognosis. Despite the high prevalence of this cancer, there is a scarcity of rigorous data from Eastern India on its relationship with known risk factors.

Objectives: The aim of this study was to evaluate the features at specific ages and gender that could play a major role in the development of oral squamous cell carcinoma.

Materials and methods: Demographics and habitual behavior were both subjected to expressive analysis. In patients with oral squamous cell carcinoma, categorical and continuous variables regarding gender were scrutinized.

Results: Age with gender cross tabs results reflects the maximum patients 245 (57.24%) were female at the age of 45-64, followed by the same age group male 480 (51.39%). The highest 654 cancer sites were found in the buccal mucosal region, and we found the total number of 349 (53.36%) were in the same age group between 45-64 years. Precisely we got the age mean±SD of 61±9 male and 64±12 female OSSC patients with statistical significance of <0.001 respectively.

Conclusion: Finally, the majority of OSCC cases in our area of eastern India were female patients who had been using gudhakhu for a long time and it was found correlating with site of OSCC in female.

Introduction

In both developed and developing countries, cancer is the top cause of mortality.[1] The oral mucosa is the most prevalent cancer site in India, according to cancer registries.[2] Tobacco use is usually connected to oral cancer in initiation of infection followed by disease progression.[3] Tobacco is widely used in India, both for chewing and smoking.[4] Because of interconnected structures, the histology of OC is crucial, so for a long period, carcinomas of the oral cavity & oropharynx were classed as OSCCs, which affected the epidemiological statistics.[5] In many ways, translational & clinical research was able to distinguish both.[6] Tumors of the oropharynx affect the root of a tongue, palatine tonsils, soft palate, or adenoids,[7] whereas OC affects the gums and alveolar ridge, the frontal 2/3rd of the tongue, buccal

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mucosa, palate, the retromolar trigone as well as hard palate.[8] Tongue and buccal mucosa cancers are the most frequent OSCC locations followed by lip and palate tumors.[5] The alcohol in-taking, smoking, various chewing habits as well as infection with significant human papillomaviruses are the risk factors for OSCC that differ by geographic region.

The most common chew intoxications are betel quid which includes tobacco, betel leaf slaked lime, and areca nut, gutka like tobacco, areca nut, slaked lime, paraffin wax, and any flavoring. Similarly, the pan masala such as slaked lime, tobacco, areca nut &musk ketones, the answer like lime, tobacco, and ash, Manipuri, tobacco, and males such as areca nut, tobacco, and lime.[9] There are around 28 recognized carcinogens in these chemicals, the most important of which arecoline, nitrosamines, tannins volatile aldehydes, nonvolatile alkaloid-derived, and flavonoids.[10,11] In Odisha, the rural people mostly women are habituated with gudakhu, which is glue-like tobacco prepared by using fine leaf dust of tobacco, sheera is known as (red soil), and the lime. Women in our state use this gudakhu for their early morning tooth brushing. Messaging the buccal area damages the epithelial cells, leading to the invasion of the carcinogenic substances to the inner tissue. All these chemicals affect the normal shape of cells, resulting in chromosomal or genetic changes. With such a high prevalence of squamous cell carcinoma in our community, there is a scarcity of data on the incidence and relationship of these practices with OSCC. So, our aim from this descriptive analysis is to understand the relationship of the OSSC cancer with age and gender, tapping importance on the habitats of the patients in eastern India.

Materials and methods

This is a retro-prospective study that has extracted data of OSCC cases from three different hospitals in eastern India from 2009 to 2019. The data were taken mainly from a dental hospital, cancer hospital, and tertiary care teaching hospital in Eastern India. Permission was granted by all heads of institutes for the retrieval of data from their archives. All Head and neck cancer involving buccal mucosa, alveolus (maxilla, mandible), gingivobuccal sulcus, solid and indulgent palate, the bottom of mouth, pharynx, larynx, and other areas of the mouth were included in this study. The retrieved data was entered into an MS Excel sheet and subjected for statistical analysis. Information gathered was assembled, and quality checks were performed. The results of the variables of interest were reported with and without confounding variables. The effect of interaction between variables of interest and confounders was also obtained to understand the validity of modifications. All the information gathered was entered into spreadsheets. For the data analysis, the statistical package for social sciences (SPSS) software version 11.0 was utilized. The tests used were t test (continuous) & chi-square (categorical).

Results

This observed based analysis was carried out and all the important correlations were obtained among 1363 total patients. The distribution of age with the gender of oral cancer patients study shows a maximum of 245 (57.24%) of females and 480 (51.39%) of the males are associated with this cancer in the age group between 45-64 years (Figure 1). Between the ages group 25-44, a total of 353 (25.89%) male and female patients. A number of 18 (i.e., 1.32% of the total number) were found in the age below 24 years. Interestingly, we observed 3 patients (0.07% of the total number) in the age group categories of 105-124 years in our study (Figure 1).

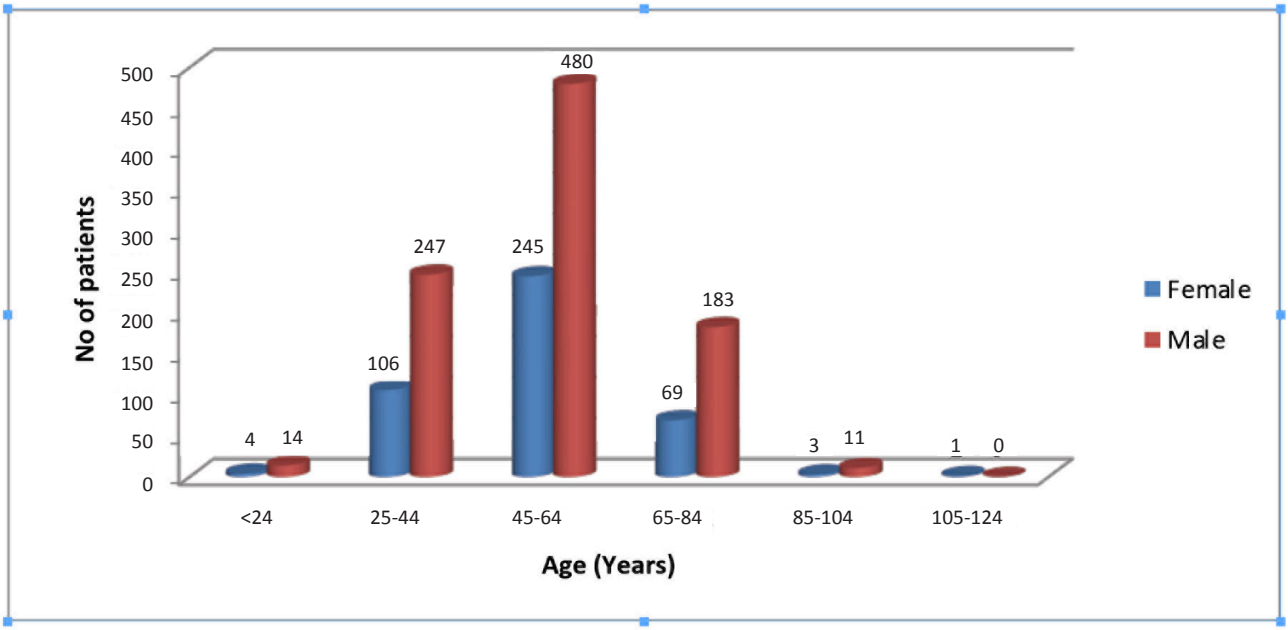

Figure 1. *Distribution of age with gender of oral cancer patient.*

As per the data of cancer distribution in different sites of the oral cavity according to different age groups of cancer cases, the highest of 654 (47.98% of the total number) is found in all age groups associated with the buccal mucosa site out of our total patient. Again, in the same age between 45-64 groups, it is found to have the highest number of cancer patient in the buccal mucosa sites. We also analyzed the data from other sites of cancer like maxilla (alveolar bone), tongue, Mandible (alveolar bone), and other parts like the floor of mouth, lips, palates, etc. (Table 1).

Table 1 Distribution of cancer in different sites of the oral cavity according to different age groups of cancer cases.

Age	Buccal mucosa	maxilla (alveolar bone)	Tongue	Mandible (alveolar bone)	Others (floor of mouth, lips, palates)	Total
<24	6 (0.91)	4 (2.51)	2 (0.68)	1 (0.59)	0 (0.00)	14 (1.02)
25-44	179 (27.37)	38 (23.89)	0 (0.00)	42 (25.14)	15 (16.3)	274 (20.10)
45-64	349 (53.36)	77 (48.42)	86 (29.53)	95 (56.88)	51 (55.43)	658 (48.27)
65-84	114 (17.43)	35 (22.01)	153 (52.57)	28 (16.76)	22 (23.91)	352 (25.82)
85-104	5 (0.76)	5 (3.14)	48 (16.494)	1 (0.59)	4 (4.34)	63 (4.622)
105-124	1 (0.15)	0 (0.00)	2 (0.68)	0 (0.00)	0 (0.00)	3 (0.22)
Total	654	159	291	167	92	1363

Table 2 The study of categorical & continuous variables about gender in patients among oral squamous cell carcinoma.

Parameter	Total	Female	Male	*p* value
	1363	428 (31.5)	935 (68.5)	
Site of Cancer				
Buccal mucosa	654	220 (33.64)	434 (66.36)	<0.001
maxilla	159	50 (31.45)	109 (68.55)	<0.001
Tongue	291	75 (25.78)	216 (74.22)	<0.001
Mandible	167	56 (33.54)	111 (66.46)	<0.001
Other	92	32 (34.79)	60 (65.21)	0.002

In Table 2, we analyzed site of cancer with respect to gender of the patients. we found most of the site were significantly differs when compared with gender of patients having oral squamous cell carcinoma. We found buccal mucosa (p<0.001), maxilla (p<0.001), Tongue (p<0.001), Mandible (p<0.001) and others site of cancer (p=0.002) were significantly differing when compared with gender of the patients. Overall, we obtained there was a significant difference between different sites of cancer when it compared with gender of patients having oral squamous cell carcinoma.in our study we observed alcohol drinking habits was high (28.60%) among the patients followed by smoking (22.10%), gutka (23.40%) and gudakhu (25.80%) (Figure 2)

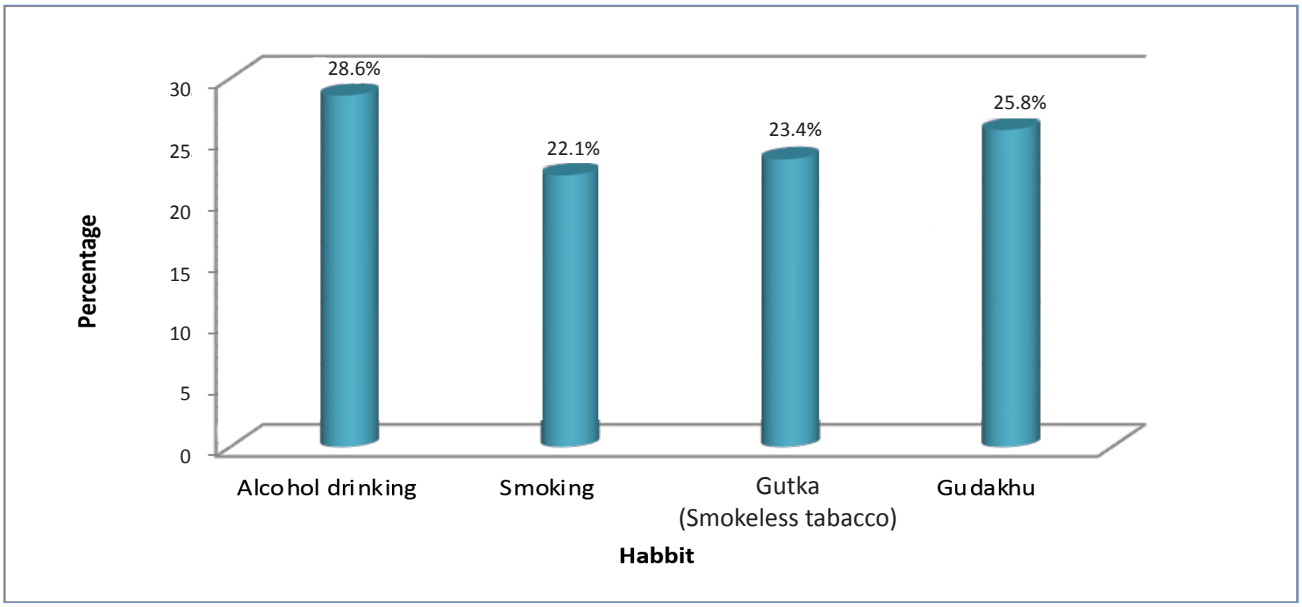

Figure 2. *Distribution of different habits.*

Discussion

Oral cancer is currently the most common type of cancer worldwide, with India accounting for about a third of the entire burden and having the second-highest number of cases. Oral squamous cell carcinoma (OSCC), which is also recognized as a recognizable pre-clinical stage of oral cancer, dominates all cases of oral cancer with potentially malignant abnormalities. OSSC is the third most common mutual cancer of squamous cell carcinoma after cervix and stomach cancer in developing nations in the South-Central and Southeast, such as India, Sri Lanka, Pakistan, and Taiwan.[12] OSSC has a complex etiology that includes chronic smoking, smokeless tobacco usage, and alcohol consumption. Chronic use of betel (pan) and tobacco, as well as alcohol, has been linked to a high risk of OC with poor oral hygiene in Southeast Asia and India.[13,14] Quantity, frequency, and duration of use of alcohol, cigarettes, gutka, and gudakhu, in addition to pan, increase the risk of OSSC. Exposure to smokeless tobacco, which contains many carcinogens, increases the risk of developing oral potentially malignant disorders.[15]

The buccal mucosa, gingiva, and buccal sulcus are much more usually affected in the oral cavity because of the use of tobacco quid such as gutka and betel quid. In a prior study, it was discovered that the micronuclei cells in smokeless tobacco users were significantly higher than in smokers. In earlier research, OSSC patients had a statistically significant increase in nuclear length, nuclear part, cell part, and nuclear-cytoplasmic percentage in oral leukoplakia and oral verrucous carcinoma compared to normal mucosa.[16,17]

In this research, the highest occurrence of OSSC was observed in the age group of 45-64 years, followed by 25-44 years, with a mean age of 63 which was consistent with previous report.[18] The male to female ratio was found to be 2:1 in this study, which was consistent with earlier research that revealed a higher incidence of tobacco use in males than females due to easier access to tobacco products. However, research on the age and gender of oral cancer patients found that the age range 45-64 years had the highest proportion of females (57.24%) and males (51.39%) (Table 1). The precise age is 63.5 years, which is also found in the study of Smith *et al*.[19] It is maybe due to the unhygienic practices of females as well as the use of gudakhu. Vigorous messaging the buccal area damages the epithelial cells, leading to the invasion of the carcinogenic substances to the inner tissue. All these chemicals affect the normal shape of cells, resulting in chromosomal or genetic changes. Although the preparation process of gudakhu is vary area-wise in general, it is glue-like tobacco prepared by using fine leaf dust of tobacco, sheera is known as molasses gerumati (red soil), and lime.

In this study, the buccal mucosa was shown to be the most affected site in both sexes, followed by the tongue & maxilla, with lips being the least common. These findings were consistent with prior research, which found that the most prevalent place was the buccal mucosa. Most of our patients used tobacco gudakhu and gutka, which could be the prevalent place for buccal mucosa. While in western countries, lungs and mouth base are considerably more prevalent because of drinking and smoking.[20]

Conclusion

In conclusion, the age factors for OSSC are a major statistical indicator in our study. Most precisely the age of 63.5 years, often accrued of the OSSC. Women's use of gudakhu along with gutka and other tobacco may be the major cause of the OSSC in eastern India. Majority of patients were male in our study, but it is an observation that females are also affected in a remarkable number which can be correlated with peculiar habit of gudakhu (snuff paste) gum message in our population. However, a study with other states of India can provide more accuracy to this observation.

Conflicts of interest

No conflict of interest exists

Source of funding

None

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The study of bone mass measurement by clavicle radiogrammetry in a comparison to the dual energy x-ray absorptiometry examination

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ABSTRACT

Background: Clavicle radiogrammetry test related to chest radiography has been found to be useful in evaluation of osteoporosis. The diagnosis of osteoporosis was based on the measurement of bone mineral density (BMD) with dual energy x-ray absorptiometry.

Objectives: The aim of this study was to evaluate bone mass measurement using clavicle radiograms to differentiate the goal standards related to the dual energy x-ray absorptiometry methods.

Materials and methods: The population sample consisted of a 100 healthy Thai adult volunteers, (50 women, 50 men) aged from 24 to 76 years. The study subjects were divided as normal bone mass group, T-score ≥ -1.0 and the low bone mass group, T-score ≤ -1.0. Subsequently, posteroanterior (PA) chest radiographs were taken. Measurements of the clavicle radiograms were evaluated, and the images at the midshaft of both clavicles were calculated. An independent t-test was used to examine the differences between the normal and the low bone mass of each gender and two separate BMD sites. The confidence interval was 95% at level of significance 0.05. Pearson's correlation was used to measure the strength and direction of linear relationship between the bone mass measurement using the dual energy x-ray absorptiometry (DEXA) test and clavicle radiogrammetry test.

Results: The results showed 18 women and 28 men maintained a normal BMD, while 32 women and 22 men had low bone mass density. The average clavicle thickness measurements of the normal bone mass of the women group were lower than the normal bone mass measurements of men. Conversely, the low bone groups of women measurements were higher than low bone mass in the men's group. A greater diminishing of cortical thickness of clavicle was found in the low bone mass than normal group for both genders. The average cortical thickness of clavicle in the low bone mass of women decreased by 17.8% (5.31 mm/6.46 mm) compared to normal women, while in men, which were fewer, 16.13% (7.07 mm/8.43 mm) between groups, respectively. The average measurements of the clavicle periosteal width and combined cortical thickness of clavicle showed a positive correlation with BMD, whereas, the clavicle endosteal width showed a negative correlation with BMD.

Conclusion: Using the radiogrammetric method to measure the clavicle cortex thickness on the chest x-ray images showed a gradual thinning of the cortex with aging. By comparison, the measurements of clavicle cortex thickness showed a moderate relationship with BMD performed by DEXA in the assessment of osteoporosis.

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Introduction

Osteoporosis, a global epidemic, has a major impact on the quality of life of individuals bone fragility. A decrease in bone strength and the changes in the bone structure causes suffering for individual of all ages. This is particularly relevant when referring to the elderly. Especially in elderly women are more likely to suffer from osteoporosis than men.[1] Previous study related to Thai people has highlighted a higher incidence of cases diagnosed with osteoporosis (1 in 3 women and 1 in 5 men).[2] The measurement of bone mineral density (BMD) with dual energy x-ray absorptiometry (DEXA) revealed osteoporosis occurred of 13.6% in the hips and 19.8% in the lower lumbar of the spine. During the process of bone growth and development, the amount of mineralised bone increases until it reaches peak bone mass which occurs around the late 20 sec or early 30 sec. Peak bone mass highest density normally transpires as a result of genetics, exercise, nutrition, and hormone levels. A slowly decline of bone mineral density occurs at which of hormone changes and aging. Peak bone mass is higher in men than women, it also higher amongst Black ethnicities compared to Asians or Whites. In general, the BMD is the highest during adolescent between the age of 30-35 years.[3] Men have a higher BMD than women around 15% to 20%. As the age increases, bone density continues to decrease slowly. The rate of bone loss is about 0.5% to 1% per year.[4-6]

According to WHO criteria, the diagnosis of osteoporosis is based on the measurement of the BMD using DEXA. The result of bone density test is evaluated according to the T-score value. T-scores value indicate the number that compared a person's bone density with those of healthy young adult of the same race, ethnicity, and gender. In this work, the T-score values are calculated based on a peak BMD reference among Asian population (Japanese database) per individuals related to gender identity. When a T-score value registers below or equal to -2.5, it is diagnosed as osteoporosis; a T-score value between -1.0 and -2.5 is diagnosed as osteopenia; a T-score greater than -1.0 is considered normal bone density.[7,8]

Clavicle radiograms using a chest x-ray image has been found to be useful and feasible in evaluation of osteoporosis.[9] A simple radiogrammetric method, image on digital radiographs, has achieved a good result related to evaluation osteoporosis compared to the DEXA scan. The radiograms offered a statistically significant correlation regarding the risk assessment of osteoporosis in the elderly population. Findings show a sensitivity level of 88.8% and 95.6%; specificity of 89.6% and 90.9%; positive predictive value of 88.8% and 95.6%; and negative predictive values of 89.6% and 90.9%, respectively. This method is supported by works performed by Delimayanti who demonstrated that the thoracic radiographic feature analysis strongly correlates with the bone density measurements using the DEXA in the assessment of osteoporosis. The method proposed in this study indicates the diagnostic test has a sensitivity of 100%, specificity of 90%, and accuracy of 97.83%.[10]

Studying the bone health in the local population is relevant for osteoporosis prevention. In a study conducted by Kruger *et al*. reported that the BMD T-score are different amongst the seven Asian countries. The highest poor bone health was observed in Vietnam for people aged 70 years, while in Thailand, the highest level of bone loss was observed in individual over 80 years of age.[11] The obvious gap in the highest level of bone loss between the two nation is concerning. Because of ethnic heterogeneity, the degree of bone loss and bone change are different. The objective of this study was to evaluate bone mass measurements on the clavicle radiograms, while providing a comparative overview of dual energy x-ray absorptiometry. We hypothesized that the distribution of bone mineral density will be different between countries. Comparison of bone density measurement between techniques will help to spot bone structure changes such as in size, thickness, or texture for Thai adults who display no symptom. However, it is recommended that individuals should monitor and follow-up bone health regularly, which would afford their medical care providers the chance to offer treatments that can reduce the severity of osteoporosis.

Materials and methods

A quantitative analysis method has been adopted in the study. This work was based on the analytical research to determine the relationship between data performed by the DEXA and the clavicle radiograms. The study was approved by the institutional review board of Naresuan university (IRB No. P10150/64). Each participant agreed to participate in the study and gave written informed consent. Recruitment and selection of participants was performed from December 2021 to April 2022 at the Regional Health Promotion Center 2, Phitsanulok Province, Thailand. All 100 participants (50 women, 50 men) were healthy Thai adults between the age of 24 and 76 years old, who live in Phitsanulok Province. Subjects with bone disorders, abnormal bone metabolism, and abnormal shape of clavicle were excluded from the study. As shown in Figure 1, information related to the parameters of the experimental procedures were presented. The BMD measurement of the lumbar vertebrae L1-L4 region and the one hip (left or right) were determined using DEXA (Hologic Discovery Wi, QDR series, USA). The BMD values were measured and reported using DEXA software at two areas of the lumbar vertebrae L1-L4 region and the one hip. According to WHO's classification, a T-score values measurement of the BMD was performed, the study subjects were divided as follows: (1) normal bone mass for those with T-score ≥ -1.0, n=46 (women=18, men=28) and (2) a low bone mass and poor bone quality (combining osteopenia and osteoporosis) for those with a T-score less than -1.0, n=54 (women=32, men=22). Subsequently, a standard digital chest posterior-to-anterior (PA) view was taken using a digital x-ray machine (Toshiba Medical Systems, KXO-50SS, Japan) with an x-ray tube voltage of 100-115 kVp and tube current of 6-8 mAs related to the Source to Image Distance (SID) of 180 cm. Image acquisition was achieved using the Konica Minolta CS7 software and Konica Minolta Aero DR unit (Konica Minolta Medical Imaging, USA). Measurements of clavicle radiogrammetry were performed at the midshaft of both clavicle bones, as described in the works by Kumar

and Anburajan.[9] All measurements were made by using the image analysis tools of the DICOM viewer (INFINITT PACS 7.0, INFINITT Healthcare Co., Ltd.). Repeated measurements were made by one researcher. These measures were performed twice and then calculated the average of those values. The bone mass imaginary chest x-ray radiogrammetry acquisition were calculated as follow:

(a) The average periosteal width of clavicle = (clavicle periosteal width $_{Right}$ + Clavicle periosteal width $_{Left}$)/2

(b) The average endosteal width of clavicle = (clavicle endosteal width $_{Right}$ + Clavicle endosteal width $_{Left}$)/2

(c) The combined cortical thickness of clavicle = (The average periosteal width - The average endosteal width)

(d) The percentage of combined cortical thickness of clavicle (%)
= (The combined cortical thickness of clavicle/ The average periosteal width of clavicle) x 100

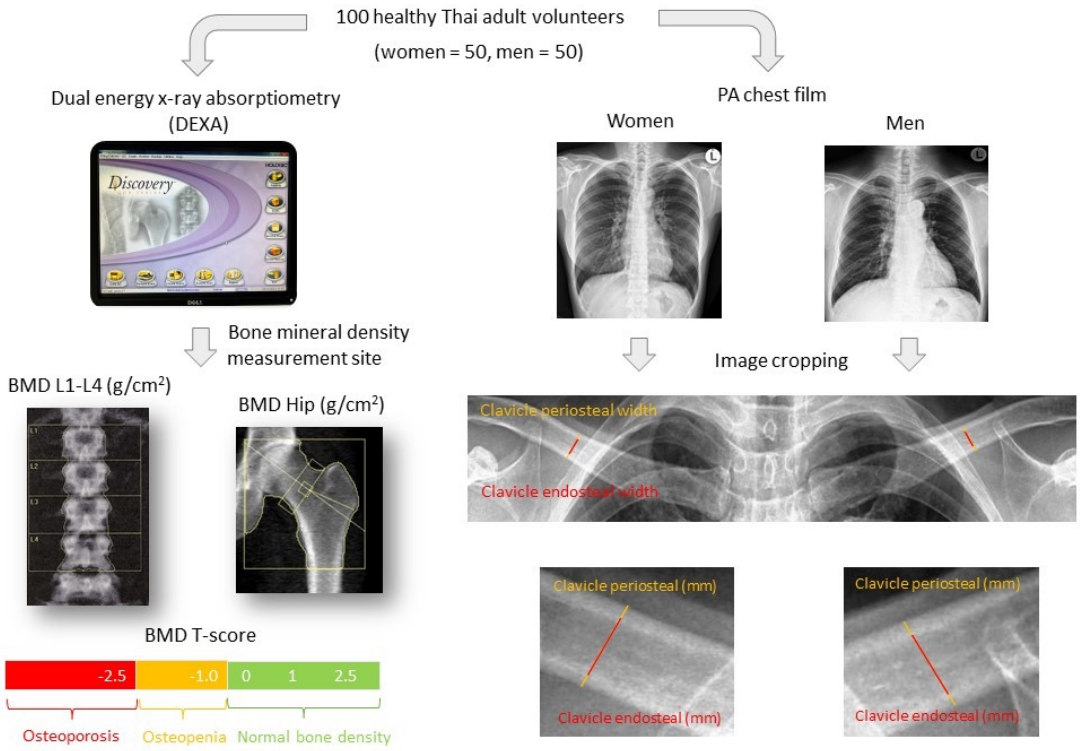

Figure 1. *The experimental procedure.*

Statistical analysis was performed using Microsoft Excel and the SPSS version 17.0 (SPSS Inc., Chicago, USA). Results were described as the mean and standard deviation (SD). An independent t-test was performed between normal and low bone mass group for each gender at the two areas in the lumbar vertebrae L1-L4 region and the one hip. Using confidence levels of 95%, a p-value less than 0.05 was considered as statistically significant. Afterwards, the Pearson's correlation analysis was used to measure the strength and direction of the linear relationship between the bone mass measurements performed by the DEXA and the clavicle radiogrammetry measured from the chest radiograph.

Results

A total of 100 healthy Thai adult volunteers received a DEXA bone density scan and a chest x-ray examination. Table 1 shows a summary of results which included relevant descriptive statistics whereby the data were expressed as mean ± standard deviation (SD) by gender and the BMD level at the lumbar vertebrae L1-L4 and the hip position. The population consisted of 50 women with a mean age of 58 ± 11.98 years (range 32-75 years), and 50 were men with a mean age of 58±12.42 years (range 24-75 years). Using diagnostic criteria regarding the severity of osteoporosis developed published by WHO, the normal BMD, T-score ≥-1.0, from 18 women and 28 men was established as standard values; Equally important, a low bone mass, T-score ≤ -1 (combination of osteopenia and osteoporosis), from 32 women and 22 men was recorded.

Data in Table 1 presents descriptive statistics of the selected participants. Men tended to have slightly higher values than women. The mean value of the weight, height, and BMI revealed diminished amounts when comparing both women and men who were found to have low bone mass values and the normal bone mass values. There was no statistically significant difference in weight, height, and BMI between the normal and the low bone mass in both

men and women (p>0.05). Measurements of the BMD using the DEXA at the lumbar area of vertebrae, the L1-L4 segments, and the hip position was significantly lower in low bone mass group when compared to the normal group (p<0.05) for both women and men. In addition, the mean value of clavicle cortex measurements, the clavicle endosteal width; the combined cortical thickness of clavicle; and the percentage of combined cortical thickness of clavicle in normal women, revealed diminished amounts when comparing between normal and low bone mass group, and it was statistically significant (p<0.05). Regarding the measured clavicle periosteal width, there was no significant difference between groups in both genders (p=0.37 in women, and p=0.10 in men).

Table 1 Demographic information, clinical characteristics, bone mineral density, and clavicle radiogrammetry relating to participants.

Variables	Total women = 50 Min-Max age (years) = 32-75				Total men = 50 Min-Max age (years) = 24-76			
		Low bone mass (n=32)				Low bone mass (n=22)		
	Normal (n=18)	Osteopenia (n=21)	Osteoporosis (n=11)	t- test (p value)	Normal (n=28)	Osteopenia (n=22)	Osteoporosis (n=0)	t- test (p value)
Weight (kg)	56.7±8.30	52.4±7.99		0.08	72.2±7.38	65.4±9.87		0.20
Height (cm)	155.1±4.87	154.5±5.42		0.69	169.2±6.60	166.4±5.48		0.11
BMI (kg/m^2)	23.6±3.74	21.9±2.99		0.08	25.3±2.78	23.6±3.51		0.07
Bone mineral density (BMD) (g/cm^2)								
BMD L1-L4	1.045±0.09	0.094±0.10		0.00*	1.097±0.11	0.875±0.09		0.00*
BMD hip	0.816±0.09	0.603±0.09		0.00*	0.861±0.14	0.674±0.06		0.00*
Clavicle radiogram on the chest x-ray film at midpoint of clavicle								
1. Clavicle periosteal width (mm)	10.47±1.78	10.18±1.05		0.37	13.46±1.20	12.86±1.32		0.10
2. Clavicle endosteal width (mm)	4.01±0.61	4.86±0.68		0.00*	5.03±0.78	5.79±0.56		0.00*
3. Combined cortical thickness (mm)	6.46±.86	5.31±0.66		0.00*	8.43±1.11	7.07±0.97		0.00*
4. Percent of combined cortical thickness (%)	61.73±3.98	52.23±4.19		0.00*	62.56±5.33	54.85±3.15		0.00*

Note: *Values are presented as mean±SD, n:number of participants, (*) indicates the p<0.05 that there is statistically significant.*

The scatter plots represent the clavicle thickness measurements from clavicle radiograms that were related to the BMD in women with normal bone mass density and women with low bone mass as shown in Figure 2 and 3. Regarding the BMD in the lower lumbar spine area (L1-L4), the results showed a moderate-to-strong correlation between the BMD levels and the clavicle radiograms on chest x-ray film (r=-0.61 to 0.77). The measurements of the clavicle periosteal width; the clavicle endosteal width; the combined cortical thickness of clavicle, (the outer minus the inner clavicle cortex); and the percentage of the combined cortical thickness of the clavicle which had positively correlated to the BMD lumbar region. Only the clavicle endosteal width showed a negative correlation to the BMD on the L1-L4 segments. Results of the hip evaluation found that the value of r varied from -0.01 to 0.75, which indicated that there was a weak-to-strong correlation. The clavicle periosteal and clavicle endosteal width showed a negative correlation with the BMD of the hip position, while the combined cortical thickness of the clavicle and the percentage of combined cortical thickness of the clavicle showed a positive correlation with the BMD of the hip position.

Regarding the patterns and trends concerning men, the clavicle thickness measurements were like that found in women. Scatter plots of clavicle thickness measurements against BMD between two groups are shown in Figure 4 and 5. In the lumbar spine, the results showed a weak-to-moderate correlation between the BMD levels and the clavicle radiograms on the chest x-ray films (r= -0.22 to 0.58). The mean value of clavicle cortex measurements, the clavicle periosteal width; the combined cortical thickness of clavicle, and the percentage of combined cortical thickness of clavicle had positively correlated with the BMD of the L1-L4 region. Only the clavicle endosteal width showed a negative correlation with the BMD of the lumbar region. In the hip position, it was found that the value of r varied from 0.30 to 0.52, which indicated that there was a weak-to- moderate correlation. The measurement of the clavicular cortical thickness such as clavicle periosteal width; combined cortical thickness of clavicle; and the percentage of combined cortical thickness of clavicle showed a positive correlation to the BMD of the hip position, while the clavicle endosteal width showed a negative correlation to the BMD hip region.

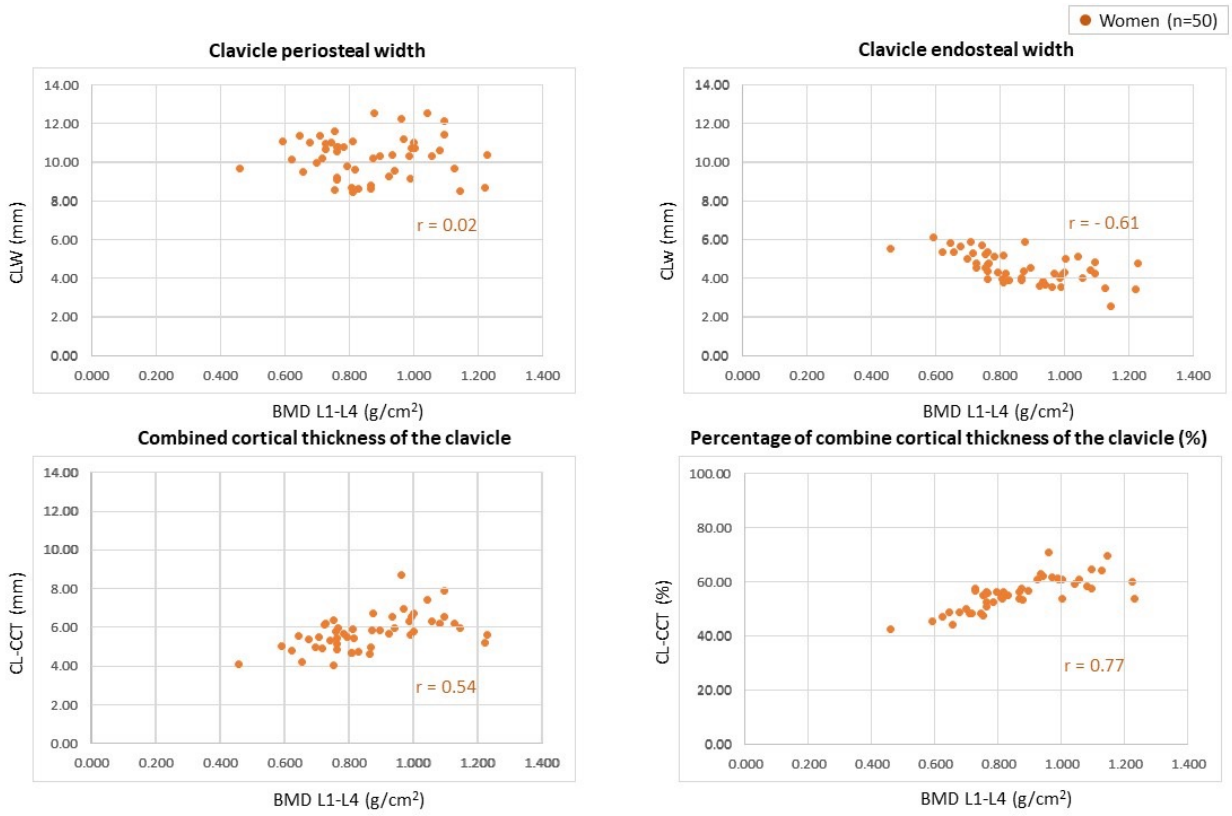

Figure 2. *Scatter plots which represent the clavicle thickness measurements from clavicle radiograms that were related to bone mineral density of the lumbar spine region (L1-L4) in women with normal bone mass and women with low bone mass. Strength of a linear relationship denotes the correlation r value.*

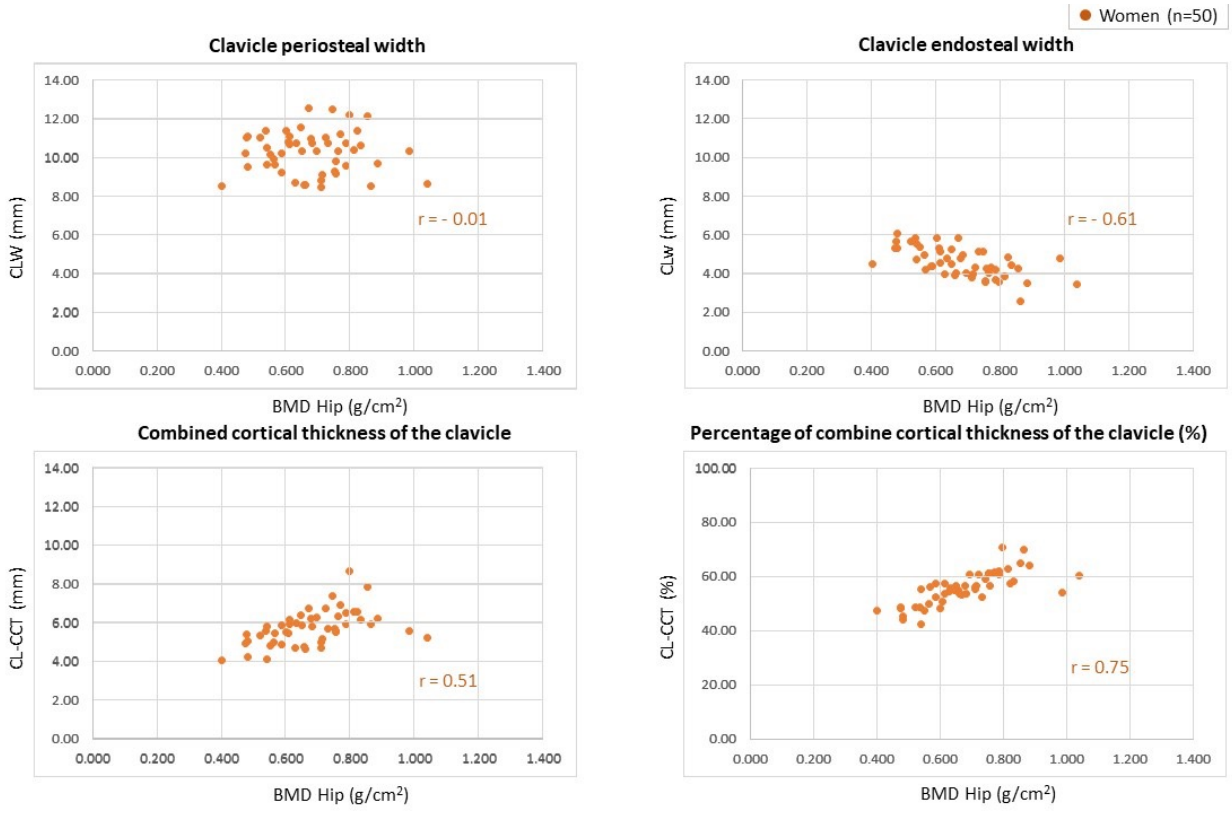

Figure 3. *Scatter plots that represent the clavicle thickness measurements from clavicle radiograms that were related to the bone mineral density of the hip position in women with normal bone mass and women with low bone mass. Strength of a linear relationship designates the correlation r value.*

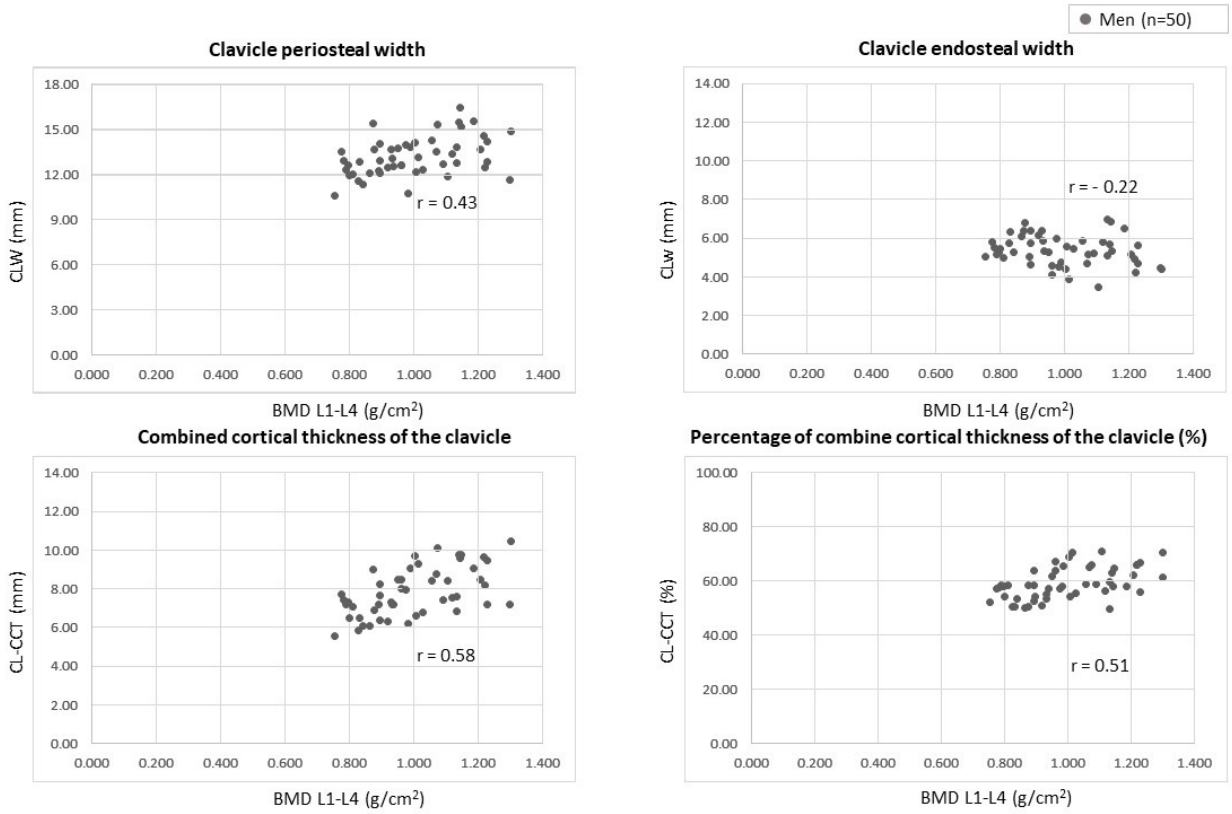

Figure 4. *Scatter plots which represent the clavicle thickness measurements from clavicle radiograms that were related to the bone mineral density of the lumbar spine region (L1-L4) in men with normal bone mass and men with low bone mass. Strength of a linear relationship indicates the correlation r value.*

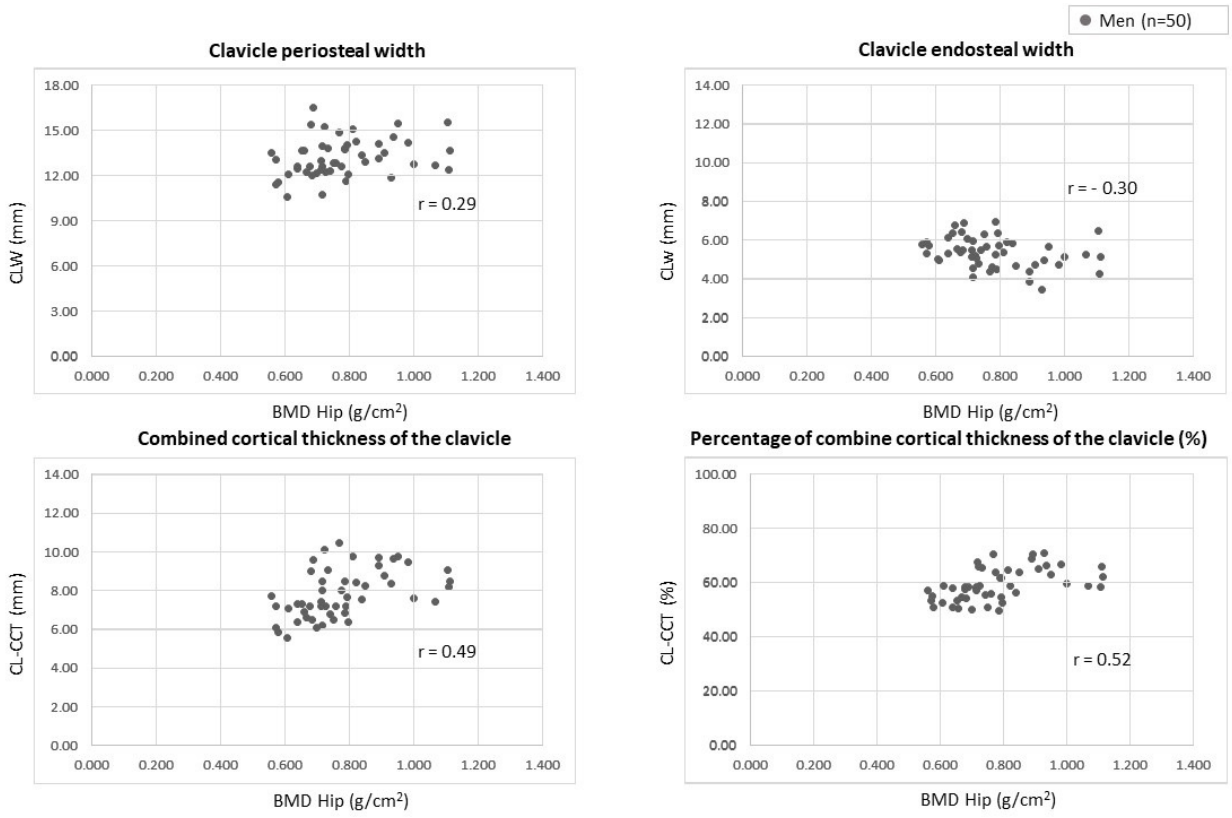

Figure 5. *Scatter plots which represent the clavicle thickness measurements from clavicle radiograms that were related to the bone mineral density of the hip position in men with normal bone mass and men with low bone mass. The strength of a linear relationship also denotes by the correlation r value.*

Discussion

Based on bone mineral density T-score, the findings indicated that the prevalence of osteopenia is higher than that of osteoporosis among participants who living in Phitsanulok Province. Regarding both women and men, as the age of individual increases, there is a reduction in the bone mass as shown in Figure 6. Elderly is associated with a decrease that effects bone mineral density T-score at both the lumbar spine and the hip position. This was particularly relevant to the BMD values at the hip joint, which were lower than the BMD at the lumbar spine. The pattern observed in our study was consistent with previous findings.[12-14]

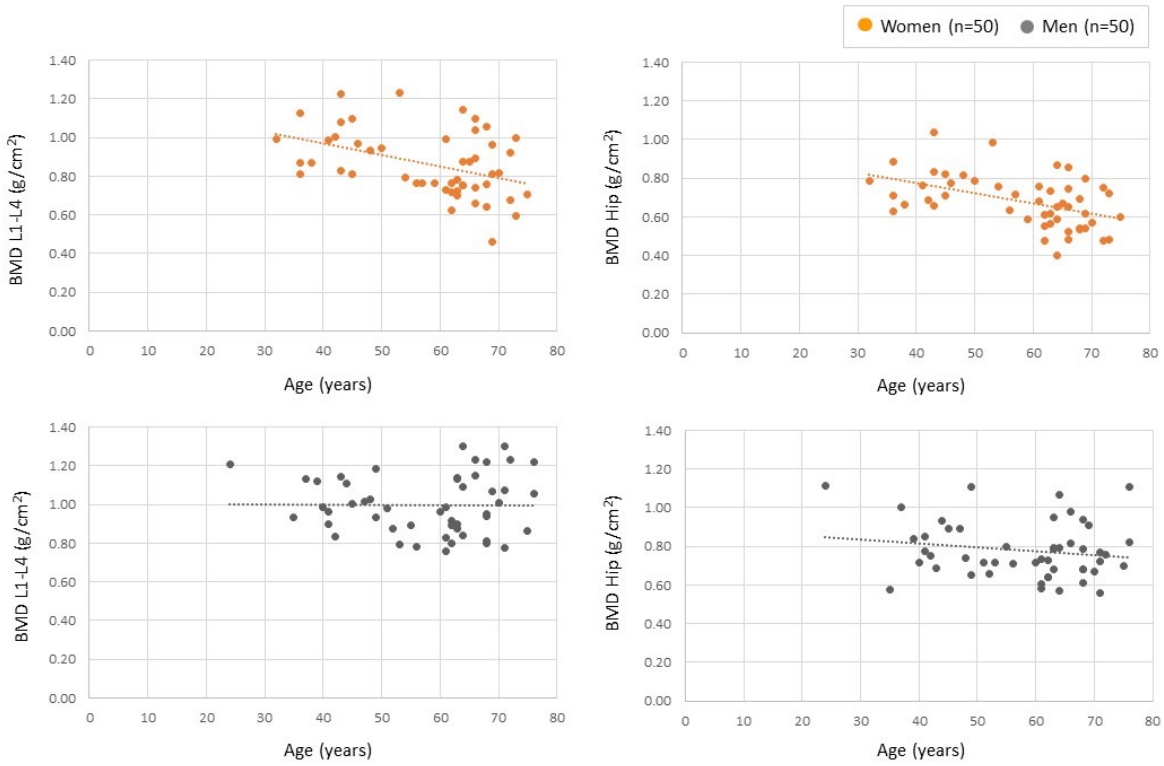

Figure 5. *Relationship between age and two separate BMD sites at the lumbar vertebrae L1-L4 segments (left), and the hip position (right) of the women participants (orange dots) and men participants (black dots).*

The demographic distribution of participant was dissimilar. The variable different according to gender, age, weight, height, BMI, and other factors associated. The lower bone mass observed in the women population than men. An explanation for these findings included menopause status that women with early menopause are having lower BMD than those with normal and late menopause.[15] However, alternative explanations regarding to the reduction of the BMD and may the influence the outcomes of weight loss, which is linked to bone loss in middle aged women.[16] Concerns regarding factors that influence bone density were broadly discussed.[17-19] However, this finding suggests that additional investigation in the demographical and clinical variables influencing BMD levels are considered.

A thinning of clavicle cortical thickness was found in the low bone mass for both genders. The measured of the clavicle periosteal width; the combined cortical thickness of clavicle; and the percentage of combined cortical thickness of clavicle showed a positive correlation concerning the BMD T-score by DEXA. Only the clavicle endosteal width showed a negative correlation with BMD. The result of clavicular cortical thickness measurements showed a decline of clavicle cortex with age in both women and men, however particularly higher in elderly individuals. A greater thinning of cortical thickness of clavicle was found in individuals with poor bone quality. Women were reported to exhibit a higher rate of bone loss than men. It was found that cortical thickness of clavicle in low bone mass women decreased by 17.8% (5.31 mm/6.46 mm) compared to normal women, while in men, there was lesser decline 16.13% (7.07 mm/8.43 mm) between groups, respectively. The average of clavicle endosteal width in normal women and low bone mass were around 4.01 mm and 4.86 mm, while in men were 5.03 mm and 5.79 mm, respectively. The average of clavicular cortical thickness obtained from experiments were observed within the range of threshold values done in south Indian woman (around 4.20 mm).[9]

The advantage of radiogrammetric method, which has been taken of the chest radiograph, can extracted essential data, which provide the medical staff with information pertaining to the clavicle cortex that influences factors such as size, thickness, texture, or shape feature in the assessment of osteoporosis. There have been few studies performed that used a combination of radiogrammetric

method with other imaging modalities. A study conducted by Maciel *et al*. found that texture attributes extracted from routine T2 sagittal Fast Spin Echo (FSE) imaging of the lumbar spine showed a positive correlated with the BMD.[20] They supported the use of quantitative analysis relating to the image texture required to predict an osteoporotic fragility fracture. However, the measurement of clavicular cortical thickness may be influenced by subject contrast and digital image quality. In future investigations, it might be possible using the plot profile instead of the straight-line measuring tool to minimize an error in the measurement.

This study has some limitations. Firstly, using opportunity sampling to recruit participants found sample sizes were unequal when relating the normal bone mass and low bone mass. There were women with osteoporosis (n=11); conversely, there no cases found for men (n=0). As a result of the low numbers of adults participating in this study, it is necessary to exclude adults aged over 75 years old in future studies. Secondly, the sensitivity, specificity, and accuracy for this study demands lengthier observation of this process. However, this study provides preliminary data to encourage the usefulness of clavicle radiograms made from a PA chest film and demonstrates the relationship between measured BMD by DEXA and clavicle radiograms variables among Thai adults.

Conclusion

The use of clavicle radiograms to measure the clavicle cortex thickness on the chest x-ray images showed a gradual thinning of the cortex with aging. By comparison, the measurements of clavicle cortex thickness showed a moderate relationship with BMD T-score from DEXA in the assessment of osteoporosis.

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Conflicts of interest

The author declares no conflicts of interest in this research.

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In vitro resistance pattern of Citrobacter infections: A retrospective study

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ABSTRACT

Background: Citrobacter infections are associated with a high mortality rate of about 33-48% if infected patients develop bacteremia. This is partly due to high prevalence of intrinsic resistance, extended spectrum beta lactamases and inducible chromosomal Amp C beta lactamases in *Citrobacter* spp. thus limiting the therapeutic options. We undertook this study to throw light on the current scenario of infection with this organism.

Materials and methods: This retrospective study was conducted over a period of 1 year in Microbiology laboratory of a tertiary care teaching hospital in Eastern part of India. From various samples, 146 clinically significant *Citrobacter* spp. identified by standard biochemical tests and susceptibility testing performed by Kirby Bauer's disc diffusion method were included in this study.

Results: Majority of patients age ranged of 41-50 year. The highest number (70/146, 47.9%) of *Citrobacter* spp. was isolated from pus and wound swabs followed by urine (46/146, 31.5%) and out of these, 51.4% strains were of *Citrobacter koseri* whereas 48.6% were of *Citrobacter fruendii*. Of *Citrobacter* isolates 36.6% were ESBL producers. They showed 54.1%, 37.9%, 47.1%, 39.8% and 58.5% resistance to imipenem, netilmycin, piperacillin tazobactam, minocycline and levofloxacin respectively. We also found 9.6% and 28.4% strains of *Citrobacter* spp. being resistant to colistin and tigecycline respectively.

Conclusion: *Citrobacter* spp. showed high degree of resistance to carbapenem and there were colistin resistance strains as well. This study reiterates the emerging resistance in these supposedly low virulence microbes which may pose future challenge in infection control activities.

Introduction

Genus *Citrobacter*, a member of family Enterobacterale has about 11 species; *Citrobacter fruendii* and *Citrobacter koseri* being the organisms of paramount clinical significance. *Citrobacter* spp. which was previously regarded as a contaminant or colonizer, is presently being associated in many infections particularly in neonates, immunocompromised adults as well as serious nosocomial outbreaks.[1,2] Various infections like urinary tract infections, wound infections, respiratory tract infections, bone infections, peritonitis, endocarditis, meningitis and bacteremia are associated with this organism.[3] Different studies attribute a 6.8% mortality in case of various Citrobacter infections patients, which can significantly increase to 17.8-56% when there is associated bacteremia.[4] The higher mortality rate may also be due to inappropriate empiric therapy of the infections caused by them as this organism is often resistant to many routinely used antibiotics

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like ampicillin-sulbactam, amoxicillin-clavulanic acid, 1st and 2nd generation cephalosporins and cephamycins.[5] These strains are potent carriers of Amp-C β-lactamase, broad-spectrum β-lactamase, extended-spectrum β-lactamase (ESBL), plasmid-mediated quinolone resistance determinants and even carbapenemase.[6] Recent emergence of multidrug-resistant strains of *Citrobacter* has resulted in longer hospital stays and higher antibiotic costs.[6] So this study was undertaken to enlighten us regarding on the current scenario of infection with this understated organism especially their pattern of drug resistance.

Materials and methods

This retrospective study was conducted in a 1000 bedded tertiary care teaching hospital in Odisha, Eastern part of India. *Citrobacter* spp. grown on aerobic cultures from various samples received in the central laboratory over a period of 1 year (March 2021 to February 2022) was considered. Various specimens like blood, bile, cerebrospinal fluid, urine, pus, wound swabs, high vaginal swabs, and body fluids were collected from patients and transported with utmost aseptic precautions in accordance with standard microbiological protocol.[7] All samples on receipt in the lab were inoculated on blood agar and Mac Conkey agar plates while urine sample was put on cystine lactose electrolyte deficient (CLED) agar. Blood and bile culture was done in BacT Alert, Biomerieux automated system which was plated on blood and Mac Conkey agar plates after being flagged positive by the instrument. Colonies received on the agar plate was examined following overnight incubation and interpreted as per clinical and Gram staining findings. Central line tip culture was considered when the same organism was isolated from blood culture as well with similar antibiotic sensitivity pattern. For respiratory samples the culture was considered when associated with correlating findings on Gram stain along with clinical evidence of infection. Only significant colony counts received on semi-quantitative in urine and respiratory culture (colony count >10^5 CFU/mL) were processes further.

Identification

Clinically significant bacteria isolated from different samples were identified by Gram staining and conventional biochemical tests as per the standard protocol.[7] The non-lactose or late lactose fermenting citrate utilizing Gram negative motile bacilli isolates with catalase, methyl red, and ortho nitro phenyl pyruvic acid test positive and oxidase, voges proskauer, phenyl pyruvic acid and lysine tests negative, were identified as genus *Citrobacter*. *Citrobacter koseri* (*C. koseri*) and *Citrobacter fruendii* (*C. freundii*) were distinguished by indole, sugar fermentation and reaction on triple sugar iron agar media. *C. koseri* is indole positive, utilizes malonate and adonitol and is K/A +G and without H_2S on TSI slant.[7]

Antimicrobial susceptibility testing

Antimicrobial susceptibility test was performed by the Kirby-Bauer disc diffusion technique on Mueller-Hinton agar and interpreted as per Clinical Laboratory Standard Institute (CLSI) guidelines.[8] The antibiotics tested were as follows (potency in µg/disc): amoxycillin-clavulanic acid (30/10), ceftriaxone (30), cefoperazone-sulbactam (75/30), ceftazidime (30), cefepime (30), piperacillin-tazobactam (100/10), imipenem (10), meropenem (10), amikacin (30), netilmycin (30), levofloxacin (5), and ofloxacin (5) minocycline (30), tigecycline(15).(Hi-Media Labs). tigecycline zone diameter was interpreted as per US FDA approved method.[9]

Quality control

Pseudomonas aeruginosa ATCC 27853, *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218 and *Klebsiella pneumoniae* ATCC 700603 were used as quality control strains for all the procedures. Antibiotic sensitivity of colistin was done using colistin broth disk elution method and interpreted as CLSI guidelines for Enterobacterales.[8]

ESBL detection

Extended spectrum β-lactamase (ESBL) screening was done for all strains by double disk potentiation test using ceftazidime (CAZ) (30 µg) and combination of ceftazidime and clavulanic acid (30/10 µg) (CAC) disk (Himedia Labs) according to the CLSI guidelines.[8]

The data was retrieved for all the samples from laboratory register. The patient's age, gender, diagnosis, site of sample collection and antibiotic sensitivity pattern were noted. The data thus retrieved was entered in MS Excel and analyzed by basic statistical methods. Probability value (*p* value) was calculated by Graph pad prism and was considered significant at $p<0.05$.

Results

During the study period out of 29,894 clinical samples processed in laboratory, 3221 (10.8%) were culture positive of which, 2024 were *Enterobactarales* alone. Among the Enterobactarale, 146 (7.2%) were clinically significant *Citrobacter* spp. These samples were from 146 patients of whom 98 were males and 48 were females. Majority of patients, 34 and 31 cases respectively, belonged to the age group of 41-50 and 51-60.

The highest number 70/146 (47.95%) of *Citrobacter* spp. was isolated from pus and wound swabs followed by 46/146 (31.5%) from urine. In the present study, 75 (51.4%) were *C. koseri* strains, whereas 71 (48.6%) were *C. fruendii* strains. There was no significant difference in isolation rate of both the species in any of the samples except for bile where all the isolates were *C. fruendii* (Table 1), 36.6% of *Citrobacter* spp. were ESBL positive. Most of ESBL positive *Citrobacter* spp. (50/51 98%) were isolated from pus and wound swabs, respiratory samples, and urine specimen. A negligible percentage was contributed by bile and other sterile body fluids (Table 1).

Among the betalactam (BL) antibiotics, *Citrobacter* spp. showed very low level of sensitivity to 3rd and 4th generation drugs (37.9% and 26.2% to ceftriaxone and cefepime respectively). Cefoperazone-sulbactam and piperacillin- tazobactam were effective in around 52% of Citrobacter infections. These organisms were rather more sensitive to aminoglycosides (69.8% sensitivity to amikacin and 62.1% sensitivity to netilmycin) than the beta lactam antibiotics. Of the quinolones, these were more sensitive to ofloxacin (57%) than levofloxacin (41.5%). But in this study, the strains of *Citrobacter* spp. were resistant to carbapenems in more than 50% cases

with susceptibility to meropenem is slightly better than that for imipenem. The strains showed maximum sensitivity to the reserve drugs, tigecycline and colistin. But cases of colistin resistant *Citrobacter* were also encountered in this study. *C. koseri* strains were more sensitive than *C. fruendii* to most of the tested antibiotics. This difference in pattern of sensitivity is significant with $p<0.05$ for netilmycin, cefepime, tigecycline and colistin (Table 2).

Table 1 Distribution of Citrobacter spp. and their ESBL pattern.

Sample	Total Number (%)	ESBL positive No (%)	*C. fruendii* (%)	*C. Koseri* (%)
Respiratory samples*	23 (15.75)	13 (25.49)	11 (15.49)	12 (0.16)
Pus and wound swabs	70 (47.95)	21 (41.18)	34 (47.89)	36 (48)
Urine	46 (31.5)	16 (31.37)	21 (29.58)	25 (33.33)
Bile	4 (2.74)	0 (0)	4 (5.63)	0 (0)
Lacrimal discharge swab	1 (0.69)	0 (0)	0 (0)	1 (1.33)
Central line tip	1 (0.69)	0 (0)	1 (1.4)	0 0 (0)
Pancreatic fluid	1 (0.69)	1 (1.96)	00 (0)	1 (1.33)
Total	146	51 (36.6)	71(48.6)	75 (51.4)

Note: **Respiratory samples include tracheal aspirate and bronchoalveolar lavage fluid.*

Table 2 Susceptibility pattern (in %) of the different *Citrobacter* spp. to antibiotics.

	AMC	AK	NET	CTR	CPM	CFS	PIT	OF	LE	MRP	IPM	MI	TGC	CL
Citrobacter spp	57.1	69.8	62.1	37.9	26.2	53.2	52.9	57	41.5	50	45.9	60.2	71.6	90.4
Citrobacter fruendii	-*	74.2	50	29.8	2.8	47.5	49.2	54.5	36.4	45.8	45.0	50.8	52.9	84.4
Citrobacter koseri	57.1	65.6	72.6	44.6	57.7	58.9	56.7	58.9	46.9	53.7	47.1	73.3	87.9	96.5
p value (at <0.05)	.-	0.29	0.012	0.12	.00001	0.31	0.412	0.66	0.39	0.37	0.83	0.018	0.00005	0.029

Note: **Intrinsic resistance to these antibiotics, AMC: amoxycillinclavulanic acid, AK: amikacin, NET: netilmycin, CTR: ceftriaxone, CPM: cefepime, CFS: cefoperazone tazobactam, PIT: piperacillin tazobactam, OF: ofloxacin, LE: levofloxacin, MRP: meropenem, IPM: imipenem, MI: minocycline, TGC: tigecycline, CL: colistin.*

Discussion

Citrobacter spp., one of the members of family Enterobacterale is a facultative anaerobic, motile, gram-negative bacillus. Only 6% of the infections attributed to family Enterobacterale is caused by this genus.[10] In the present study *Citrobacter* spp. accounted for 7.2% of the infection among various Enterobacterale.

It can cause infections like Urinary tract infection, bacteremia, meningitis, pneumonia, osteomyelitis, peritonitis, and endocarditis when the host defenses are breached.[11] The bacteria in the present study were most isolated from pus and urine. This is similar to findings by Mohanty *et al*[12] but in contrast other studies by Khanna *et al*.[11] and Samonis *et al*.[13] report pus as the commonest sample.

Citrobacter bacteremia is associated with a high mortality rate between 33% and 48%.[5,14] But in the present study, no case of bacteremia was detected as supported from studies by other workers.[12,15] This may be due to the fact that in this study only a tiny proportion of samples belonged to extreme age groups where the bacteremia is classically seen.

Citrobacter spp. causes of infections in neonates particularly in NICU.[16] In a study by Lipsky *et al*.[9] most of the infected patients were elderly, and nearly all had significant underlying illnesses. But in the present study 41-50 year was the most common age group of isolation of this organism. Male predominance was seen in this study which had been reported by other studies also.[12] *C. freundii* and *C. koseri* are the two most common pathogens and infections can be acquired from exogenous as well as endogenous sources, being ubiquitous in nature as a saprophyte in soil and sewage and as a commensal in human gastrointestinal tract. In the present study although *C.koseri* (51.4%) outnumbered *C. fruendii* (48.6%), there was no significant difference in rate of isolation of both the species. In the study done by Metri *et al*.[17] from Southern India, of the 563 isolates of *Citrobacter* spp., *C. koseri* was in 70% of samples. Similarly, in another study[12] from Northern India, *C. koseri* (90.2%) far exceeded *C. freundii* (9.8%) cases. But contrasting to these Mohan *et al*.[18] found *C. fruendii* as the predominant species and majority being isolated from pus samples. Mohan *et al*.[18] also isolated rarer species like *C. farmeri* (8.2%), *C. braakii* (5.4%), *C. werkmanii* (5.4%) and *C. gilleni* (3.4%) which were not reported in other studies. In a previous study, these fewer common species have also been proved as potential pathogens.[19]

Prevalence of ESBL in *Citrobacter* spp. worldwide was reported to be 0.5-36%.[20,21] In this study, 36.6% of *Citrobacter* isolates were ESBL producers. But this is strikingly different from few studies from India where the prevalence of ESBL is much higher; 61.6% in study by Khanna *et al*. and

80.9% in study by Praharaj *et al*.[11,22] It is generally recognized that patients infected with ESBL-producing organisms are at risk for poor outcome.

These organisms are intrinsically resistant to multiple antibiotics thus narrowing their treatment options. Both the *Citrobacter* spp. are resistant to ampicillin while *C. fruendii* is resistant to ampicillin-sulbactam, amoxicillin-clavulanic acid, 1st and 2nd generation cephalosporins and cephamycins. In this study, these antibiotics were reported as resistant upon confirming identification and excluded from further analysis. Among the other tested antibiotics, sensitivity to aminoglycosides was around 60%, with 69.8% for amikacin and 57.1% for netilmycin. Sensitivity for third and fourth generation cephalosporins (37.9% for ceftriaxone and 26.2% for cefepime) had a very dismal performance. Among the flouroquinolones tested, ofloxacin was more sensitive (57%) than levofloxacin (41.5%). Similar findings have also been noted by other studies.[12,23]

Other previous studies have stated carbapenems and beta-lactam/beta-lactamase inhibitor combinations appear to be promising alternatives.[24,25,26] But present study negates this finding as in this tertiary care set up, carbapenem resistance was seen in about 50% cases. A similar lower degree of susceptibility to carbapenems was noted in about 80% cases in another study.[12] Among beta lactam combination agents cefoperazone-sulbactam and piperacillin-tazobactam were effective with sensitivity in 53.2% and 52.9% strains respectively. In this study, there were strains where resistance to the known reserve drugs tigecycline and colistin was seen. Colistin resistance in this species is not yet reported in literature. Further analysis of the colistin resistant strains was not possible because of the retrospective nature of this work which may be considered as a limitation of the study.

Citrobacter is thought of as a commensal flora of intestine but presence of this low virulence yet resistant bacteria in hospitalized patients may complicate surveillance and infection control efforts.[5] Present study illustrates the high degree of drug resistance in this organism. There is a high prevalence of carbapenem resistance in *Citrobacter* spp., which is a cause of concern. Although other Gram negative Enterobacterales, *E. coli* and *Klebsiella* spp. have been major multi drug resistant pathogens, but probably this genus is not far behind. Colistin resistance is being noted in strains of *Klebsiella* spp. but further molecular studies are needed to characterize the colistin resistance in this genus. As *Citrobacter* is also a part of fecal flora further surveillance of the resistance genes to block dissemination of the organism in hospital environment is the need of the hour.

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Conflicts of interest

The authors declare there is no conflict of interest among them.

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Ethics Statement

No ethical approval required in this Study.

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Potential toxicity of wild *Ipomoea* ingested by schoolchildren in remote Northeastern Thailand

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ABSTRACT

Background: Natural plant toxins can cause food poisoning upon intentional or unintentional consumption of wild plants. Some toxic wild plants can be mistaken for edible species because of their morphological resemblance. This study examined a poisoning case report of schoolchildren who consumed a steamed tuberous root of wild *Ipomoea*, misidentified as *I. mauritiana*, and experienced gastrointestinal toxicity.

Objectives: This study aimed to identify the tuberous root of wild *Ipomoea* using the internal transcribed spacer (ITS) region as a DNA barcode and characterize compounds obtained using gas chromatography-mass spectrometry (GC-MS).

Materials and methods: DNA was extracted from fresh and cooked samples of the storage root. PCR amplification and DNA sequencing of the entire ITS region were performed. FastTree and maximum likelihood analyses were used to obtain phylogenetic trees of the *Ipomoea* species. Root extracts were prepared for GC-MS analysis, and potentially harmful phytochemicals responsible for poisonous plant exposure were predicted based on a well-established plant toxin database.

Results: ITS phylogeny showed a close relationship between wild toxic *Ipomoea* and edible *I. mauritiana*. The chemometric profile obtained from GC-MS analysis of the root extracts revealed the presence of 31 phytochemicals. Among them, two putatively toxic compounds identified were β-amyrin and coumarin.

Conclusion: Misidentification of the wild poisonous plant reported herein resulted in toxic plant ingestion. Although most poisonous plant exposures are not life threatening, measures should be taken to ensure the safety of the general public.

Introduction

Wild plant foraging is crucial for survival in many parts of the world. Vulnerable communities living in remote areas may rely on wild edible plants that are naturally grown or reproduced for consumption and medicinal use. All parts of the plant, including leaves, stems, flowers, fruits, roots, and tubers, can be used.[1-3] Tuberous roots of many plants play a vital role in the human diet as a source of carbohydrates, and they are a staple food for some indigenous people.[4] Sweet potato which belongs to the genus *Ipomoea* (family *Convolvulaceae*) can be gradually harvested as a food crop over a long period of time.[5] Within this large pantropical genus of approximately 800 species, mostly having wild origins, more than 70 species have tuberous roots, of which only 24 are edible.[6-8] For some species, the tuberous roots are morphologically indistinguishable and misidentification of palatable and poisonous plants can occur.

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Plants contain several non-nutrient phytochemicals that are synthesized as secondary metabolites. Compounds such as phenolics, alkaloids, and terpenes are important for plants to cope with biotic and abiotic stresses but may exhibit phytotoxic activity as a result of their defensive properties.[9,10] Plant toxins can be classified into four groups based on their resultant toxidromes: cardiotoxic, neurotoxic, cytotoxic, and gastrointestinal/hepatotoxic.[11] In Thailand, a 10-year retrospective analysis of plant poisoning cases revealed that the gastrointestinal toxidrome was most frequently encountered. In a total of 2,901 poisonous plant exposure cases, 69.8% involved children aged under 13 years. Most cases were caused by *Jatropha curcas*, and *Manihot esculenta* was the most common cause of death.[12] The present study involved a case of unintentional ingestion of the storage root of an unknown species of *Ipomoea*, which consequently led to food poisoning in schoolchildren. The morphology of this wild tuberous root resembled that of edible *I. mauritiana*. Hence, the objectives of this study were to (i) identify the tuberous root of wild *Ipomoea* using the internal transcribed spacer (ITS) region as a DNA barcode to reconstruct phylogenetic trees; and (ii) characterize compounds obtained using gas chromatography-mass spectrometry (GC-MS) and identify putative phytotoxins present in the storage root of wild *Ipomoea* based on a well-established plant toxin database.

Materials and methods

Clinical plant samples

A fresh tuberous root sample and remaining portions of cooked sample obtained from a clinically reported case were delivered to the Toxicology Center, National Institute of Health (voucher specimens: DMSC24649 and DMSC24650). The storage root was collected from a rural area in Sisaket Province, Northeastern Thailand. It was initially identified as giant potato, a common name for *I. mauritiana*, which is palatable and used in traditional medicine. After dividing the root into halves, one half was further cut into cubes and used to prepare a steamed dish for the schoolchildren.

DNA extraction, PCR amplification and DNA sequencing

This case was reported as unintentional toxic plant ingestion due to misidentification of the wild tuberous root of *Ipomoea* (Figure 1). Based solely on its appearance without other diagnostic characters, such as leaves and flowers, the morphology of this tuberous root resembled that of edible *I. mauritiana*. Thus, molecular approaches were employed to confirm the taxonomic entity of the root.

Twenty milligrams of each fresh and cooked samples were ground to a fine powder under liquid nitrogen. DNA was extracted using the DNeasy™ Plant Mini Kit (QIAGEN, Germany) according to the manufacturer's instructions. DNA samples were quantified using a NanoDrop UV-Vis spectrophotometer (Thermo Fisher Scientific, USA), and diluted to a final concentration of 30 ng/µL. PCR amplification and DNA sequencing of the entire ITS region were performed using ITS1 forward primer and ITS4 reverse primer.[13] Each PCR reaction of 25 µL contained 9.5 µL of OnePCR™ master mix with fluorescence dye (GeneDireX®, Taiwan), 2.5 µL of 10 µM of each primer, 1 µL of DNA template, and 9.5 µL of nuclease-free water. The amplification was performed using Mastercycler Gradient 5331 (Eppendorf, Germany) under the following conditions: initial denaturation at 95°C for 2 min, followed by 30 cycles of denaturation at 95°C for 1 min, annealing at 55°C for 1 min, extension at 72°C for 1 min, and final extension at 72°C for 5 min. PCR products were examined using 2% (w/v) agarose gel electrophoresis, and cleaned using the QIAquick PCR Purification Kit (QIAGEN, Germany). Sanger sequencing of the purified amplicons was performed at the Toxicology Center, National Institute of Health, Ministry of Public Health, Thailand.

Figure 1. *Fresh tuberous root sample of wild Ipomoea collected from a rural area in Sisaket Province, Northeastern Thailand.*

Phylogenetic analyses

The ITS sequences generated from both fresh and cooked plant samples were aligned with other derived sequences of *Ipomoea* species containing storage roots using Geneious Prime 2021.2.2 (https://www.geneious.com).[7] FastTree 2.1.11 was also performed in Geneious Prime to generate an approximately-maximum-likelihood phylogenetic tree using the GTR model and to compute local support values with the Shimodaira-Hasegawa (SH) test.[14] SH-like support was estimated using 1,000 resamples. Maximum likelihood (ML) analysis on the other hand, was conducted on the CIPRES Science Gateway portal using RAxML 8.2.12 with the GTRGAMMA model.[15] Branch support was estimated using 1,000 bootstrap replicates. The phylogenetic trees were depicted using FigTree 1.4.3 (http://tree.bio.ed.ac.uk/software/figtree), and clades that received SH-like support ≥0.90 and bootstrap support ≥70% were considered strongly supported.

Preparation of root extracts for GC-MS analysis

Twenty-five grams each of fresh and cooked tuberous root samples were washed thoroughly with running water and left to dry at 25°C. The samples were ground and extracted with water and dichloromethane (1:1), followed by addition of anhydrous sodium sulphate. In addition to the neutral fraction obtained, acidic and basic fractions were prepared. The acidic fraction (pH ~3-4) was obtained by acidifying with 6N HCl, whereas the basic fraction (pH ~9-11) was obtained by basifying with NH_4OH. All three fractions from both fresh and cooked sample extracts were filtered, and the filtrates were evaporated to dryness under a nitrogen stream. The residues were dissolved in ethyl

acetate and filtered using syringe filters (13 mm diameter) with hydrophilic PVDF membranes (0.2 µm pore size) (VertiPure™ PVDF-HL, Thailand). Six separate filtrates were subjected to GC-MS analysis.

GC-MS analysis and identification of putative plant toxins

The filtrates containing secondary metabolites from the root extracts of wild *Ipomoea* were analysed using an Agilent 7890A/5975A GC-MS (Agilent Technologies, Santa Clara, CA, USA). Separation of the compounds was performed using an analytical HP-5MS column (30 m × 0.25 mm, 0.25 µm film thickness) coated with 5% phenyl-methylpolysiloxane (Agilent Technologies). The column temperature was programmed as follows: 70°C for 0.5 min, rising to 150°C at a rate of 10°C/min for 10 min, and 310°C at a rate of 25°C/min for 10 min. Helium was used as the carrier gas at a flow rate of 1 mL/min. The sample injection volume was 1 µL. The temperatures of the injection and detector were adjusted to 250°C and 280°C, respectively. The MS operating conditions included electron ionisation mode of 70 eV and ion source temperature of 250°C. Data processing and acquisition were performed using Agilent G1701EA MSD Productivity ChemStation software (Agilent Technologies). GC-MS profiling of the secondary metabolites was performed using the NIST 17 mass spectral library (National Institute of Standards and Technology, USA). To ensure that the tuberous root samples were not contaminated with organic chemicals such as pesticides, the Agilent RTL pesticide and endocrine disruptor MS library (RTLPEST3.L, Agilent Technologies) was also employed. All detected compounds were compared against the Toxic Plants-PhytoToxins database, which is a compilation of 1,586 phytotoxins obtained from 844 plant species.[16]

Results and discussion

Poisoning symptoms

Nine schoolchildren (9-10 years of age) consumed portions of the tuberous root of wild *Ipomoea* after steaming. Within 30 min to 4 hrs, they experienced symptoms of poisoning, including nausea, vomiting, abdominal pain, and dizziness. The symptoms were similar to those reported in Sri Lankan villagers who misidentified toxic *I. asarifolia* as the leafy vegetable *I. aquatica*.[17] Other cases of poisoning from ingestion of *Ipomoea* have occurred in livestock, with specific phytotoxic substances, such as ergoline alkaloids in the leaves of *I. asarifolia*, ipomeamarone in the storage roots of *I. batatas*, and swainsonine in *I. carnea*.[18–20]

Phylogenetic analyses

In this study, two ITS sequences of fresh and cooked tuberous root samples were generated from their respective PCR products and submitted to GenBank (accession numbers OM030216 and OM030217). An aligned matrix of 656 characters was constructed using 65 other sequences of *Ipomoea* species retrieved from GenBank and a sequence for *Solanum tuberosum* as outgroup. Both FastTree and ML analyses produced a congruent tree topology. Thus, only the ML tree (*lnL* = -6842.6) with SH-like support ≥0.90, bootstrap support (BS) ≥70%, and edibility status of the *Ipomoea* members is shown. Phylogenetic placement of both fresh and cooked samples of wild *Ipomoea* revealed a close relationship with edible *I. mauritiana* (SH-like =0.95; BS =97%) (Figure 2).

Several species of *Ipomoea* have been reported to possess health benefits and are cultivated as food plants.[21,22] Of the 36 *Ipomoea* species currently known from Thailand, nine species (with tuberous roots) are edible.[23-25] The large storage root of wild *Ipomoea* obtained in this study was morphologically similar to that of *I. mauritiana* and was, therefore, misidentified as edible. Misidentification of poisonous plants as common edible plants or indigenous medicinal herbs was one of the main causes of poisoning, as previously noted to occur with the schoolchildren at a remote primary school in the northern part of the country.[26]

GC-MS analysis

GC-MS analysis of fresh and cooked root extracts of wild *Ipomoea* revealed chromatograms of the acidic, basic, and neutral fractions (Figure 3). In all fractions, the corresponding chemical constituents were identified based on their peak retention time, peak area (%), and quality matching of the compounds (>90%) to those of known compounds described in the NIST library. A total of 31 distinct compounds were detected (Table 1). Notably, based on the chemometric profiles, a diterpenoid and triterpenoids were found only in the fresh sample extract, whereas a coumarin, an n-alkane, and lipid-soluble compounds were present in the cooked sample extract. Other phytochemicals, including a flavonoid, a fatty amide, a fatty alcohol, phytosterols, and fatty acids, were present in both extracts. These results support the findings of a previous study by Viji and Paulsamy, who obtained 27 bioactive compounds from the acetone extract of the tuberous roots of *I. mauritiana* using GC-MS.[27] In the present study, no compound was matched with those present in the Agilent RTL pesticide and endocrine disruptor MS library, indicating the absence of residual pesticides and other organic chemical contaminants from the environment.

Identification of putative plant toxins

All 31 compounds detected via GC-MS were compared against the Toxic Plants-PhytoToxins database.[16] The results revealed two chemical compounds in the wild *Ipomoea* samples that could potentially exhibit toxicological properties. These were triterpenoid (β-amyrin), present in the fresh sample extract, and coumarin (scopoletin), which was found in the cooked sample extract. Quantitatively, the GC-MS profile revealed the highest peak area for scopoletin (12.11%) in the neutral fraction of the cooked sample extract (Table 1).

Scopoletin, a thermally stable phenolic compound with a low molecular weight, has been found in different plant families. This compound plays an important role in traditional medicine in Africa, Asia, and Europe.[28] Scopoletin is biosynthesized from the phenylpropanoid pathway, and its synthesis can be induced in response to plant exposure to biotic and abiotic stresses such as pathogen infection, tissue damage, drought, heat, and cold.[29,30] It can accumulate in the roots, especially under iron-deficient conditions.[30,31] In addition to plant defense, scopoletin and other coumarins are also reported to have insecticidal and acaricidal effects.[32-34] Such biopesticide activities could result in potential negative health impacts on animals. Although without previous

reports of human evidence, it is known that swallowing the chemical product of scopoletin can lead to gastrointestinal disorders involving nausea and vomiting.[35] However, the degree of toxicity may depend on the quantity of the substance and individual sensitivity. Further investigations involving toxicity assessments using bioassays are required.

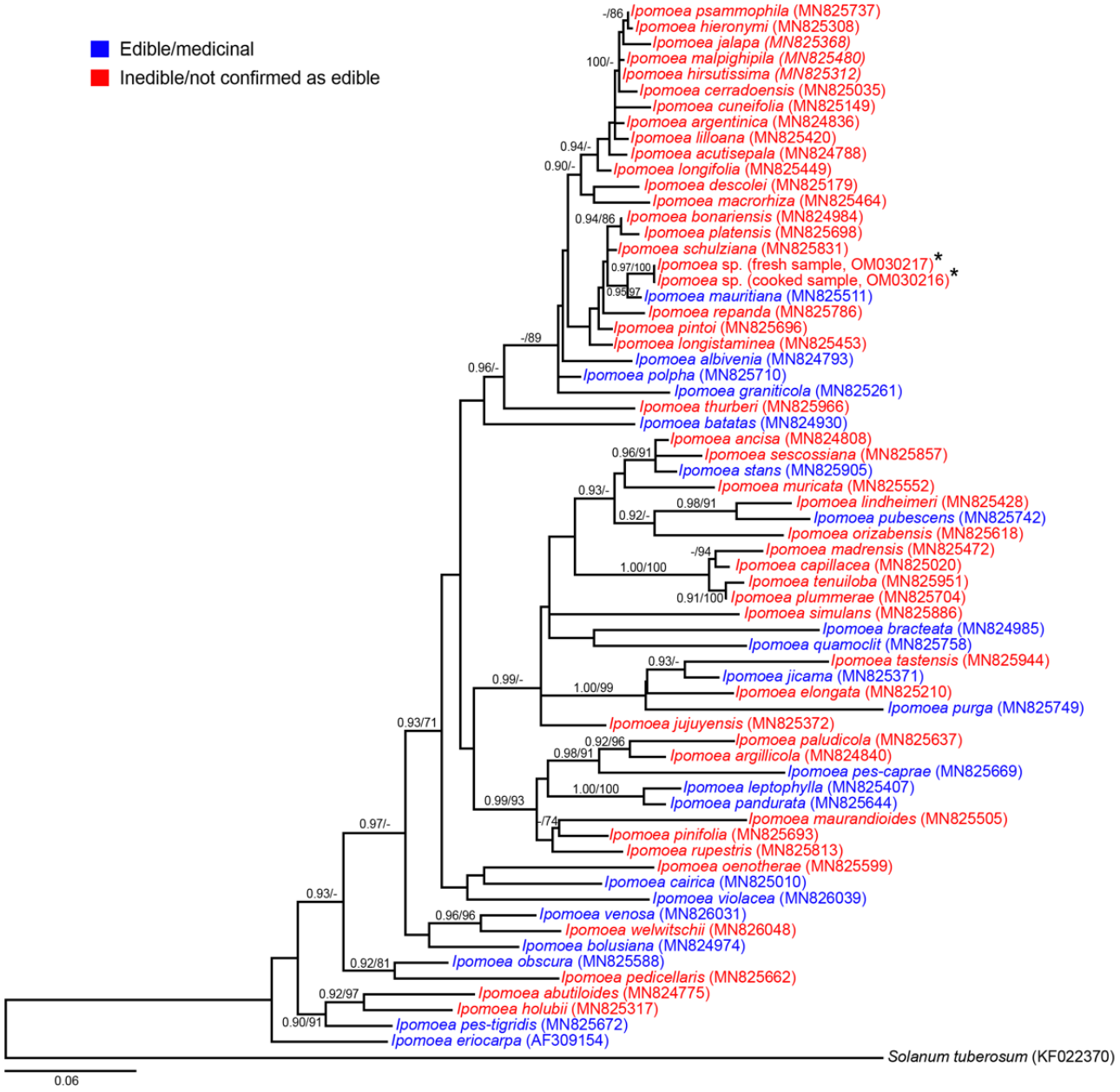

Figure 2. *ITS phylogeny based on ML analysis reveals relationships of Ipomoea species with tuberous roots. SH-like support (≥0.90) and bootstrap support (≥70%) are shown above the branches. GenBank accession numbers are provided in parentheses. *plant samples used in this study.*

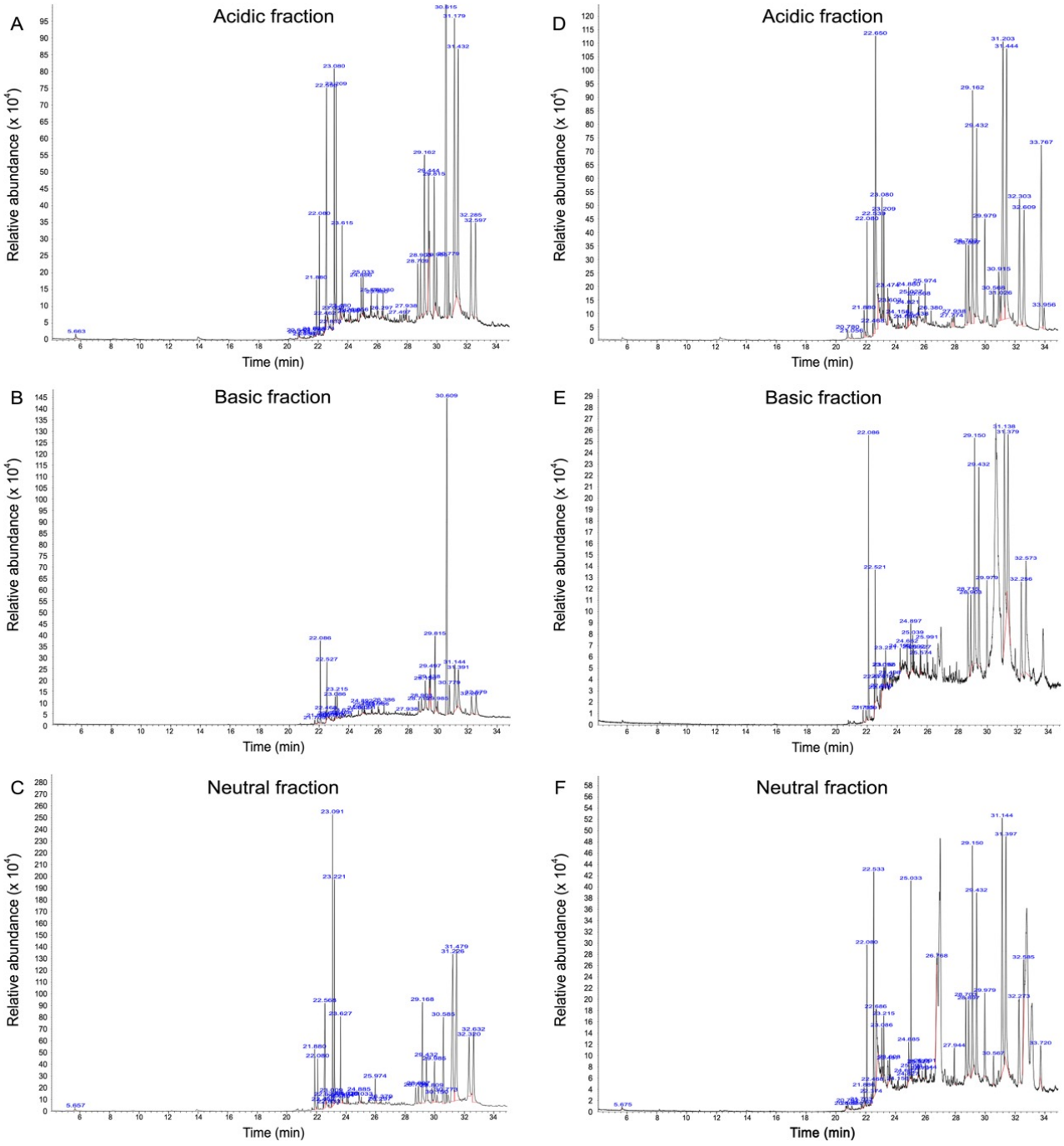

Figure 3. *GC-MS chromatograms of wild Ipomoea obtained from root extracts of fresh (A-C) and cooked samples (D-F). In both types of sample extracts, chemical compounds were detected in acidic, basic, and neutral fractions.*

Table 1 List of compounds identified by GC-MS analysis in fresh and cooked samples of wild *Ipomoea* tuberous root.

Sample	Fraction	Compound detected	Formula	m/z	Retention time (min)	Peak area (%)	Quality matching (%)	Nature of compound
Fresh tuberous root	Acidic	Tetradecanoic acid	$C_{14}H_{28}O_2$	228	20.645	0.17	96	Fatty acid
		Pentadecanoic acid	$C_{15}H_{30}O_2$	242	21.75	0.11	95	Fatty acid
		(E)-5-Octadecene	$C_{18}H_{36}$	252	21.88	1.08	91	Fatty acid
		7,9-Di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	$C_{17}H_{24}O_3$	276	22.08	1.67	99	Flavonoid
		Palmitic acid	$C_{16}H_{32}O_2$	256	22.556	6	98	Fatty acid
		n-Nonadecanol-1	$C_{19}H_{40}O$	284	23.009	0.25	93	Fatty alcohol
		9-Octadecen-1-ol, (Z)-	$C_{18}H_{36}O$	268	23.08	4.04	99	Fatty acid
		Linoleic acid	$C_{18}H_{32}O_2$	280	23.48	0.1	98	Fatty acid
		Stearic acid	$C_{18}H_{36}O_2$	284	23.615	1.86	99	Fatty acid
		Erucamide	$C_{22}H_{43}NO$	337	25.98	0.38	91	Fatty amide
		Campesterol	$C_{28}H_{48}O$	400	28.709	1.7	98	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.444	2.65	99	Phytosterol
		Olean-12-en-3-ol, acetate, (3.beta.)-	$C_{32}H_{52}O_2$	468	30.779	2.01	99	Triterpenoid
	Basic	7,9-Di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	$C_{17}H_{24}O_3$	276	22.086	4.38	95	Flavonoid
		Palmitic acid	$C_{16}H_{32}O_2$	256	22.527	4.01	94	Fatty acid
		1,13-Tetradecadiene	$C_{14}H_{26}$	194	23.086	1.32	93	Fatty acid
		Stearic acid	$C_{18}H_{36}O_2$	284	23.621	0.21	96	Fatty acid
		Campesterol	$C_{28}H_{48}O$	400	28.715	1.37	95	Phytosterol
		Stigmasterol	$C_{29}H_{48}O$	412	28.903	1.31	90	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.438	1.39	91	Phytosterol
		β-Amyrin	$C_{30}H_{50}O$	426	30.779	3.06	93	Triterpenoid
	Neutral	n-Heptadecanol-1	$C_{17}H_{36}O$	256	21.88	2.2	91	Fatty alcohol
		7,9-Di-tert-butyl-1-oxaspiro(4,5) deca-6,9-diene-2,8-dione	$C_{17}H_{24}O_3$	276	22.08	1.47	98	Flavonoid
		Palmitic acid	$C_{16}H_{32}O_2$	256	22.568	5.68	99	Fatty acid
		Cyclohexadecane	$C_{16}H_{32}$	224	23.009	0.42	99	Fatty acid
		1,9-Tetradecadiene	$C_{14}H_{26}$	194	23.091	8.26	99	Fatty acid
		Docosanoic acid	$C_{22}H_{44}O_2$	340	23.221	6.39	91	Fatty acid
		10(E),12(Z)-Conjugated linoleic acid	$C_{18}H_{32}O_2$	280	23.48	0.2	95	Fatty acid
		Stearic acid	$C_{18}H_{36}O_2$	284	23.627	3.25	99	Fatty acid
		E,E,Z-1,3,12-Nonadeca-triene-5,14-diol	$C_{19}H_{34}O_2$	294	24.038	0.27	91	Fatty acid
		1,2-Diethylcyclohexadecane	$C_{20}H_{40}$	280	24.133	0.28	94	Fatty acid
		Erucamide	$C_{22}H_{43}NO$	337	25.974	0.92	95	Fatty amide
		Campesterol	$C_{28}H_{48}O$	400	28.709	0.96	98	Phytosterol
		Stigmasterol	$C_{29}H_{48}O$	412	28.897	0.97	99	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.432	3.08	99	Phytosterol
		2,6-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-1,1,4a-trimethyl-7-(1-methylethyl)-, monomethyl ether,[2S-(2. alpha.,4a.alpha.,10a.beta.)]-	$C_{21}H_{32}O_2$	316	29.809	0.91	90	Diterpenoid

Table 1 List of compounds identified by GC-MS analysis in fresh and cooked samples of wild *Ipomoea* tuberous root. (continue)

Sample	Fraction	Compound detected	Formula	m/z	Retention time (min)	Peak area (%)	Quality matching (%)	Nature of compound
Cooked tuberous root	Acidic	1-Hexadecanol	$C_{16}H_{34}O$	242	21.886	0.61	91	Fatty alcohol
		7,9-Di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	$C_{17}H_{24}O_3$	276	22.08	3.4	95	Flavonoid
		Palmitic acid	$C_{16}H_{32}O_2$	256	22.533	6.45	98	Fatty acid
		Scopoletin	$C_{10}H_8O_4$	192	22.686	5.47	97	Coumarin
		1,9-Tetradecadiene	$C_{14}H_{26}$	194	23.086	1.06	95	Fatty acid
		Cyclopentadecane	$C_{15}H_{30}$	210	23.215	1.59	97	Fatty acid
		Campesterol	$C_{28}H_{48}O$	400	28.703	2.63	99	Phytosterol
		Stigmasterol	$C_{29}H_{48}O$	412	28.897	2.83	97	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.432	6.78	99	Phytosterol
	Basic	(Z)-7-Hexadecene	$C_{16}H_{32}$	224	21.909	0.4	91	Fatty acid
		7,9-Di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione	$C_{17}H_{24}O_3$	276	22.086	6.59	98	Flavonoid
		Palmitic acid	$C_{16}H_{32}O_2$	256	22.521	5.27	99	Fatty acid
		Scopoletin	$C_{10}H_8O_4$	192	22.95	0.34	96	Coumarin
		Campesterol	$C_{28}H_{48}O$	400	28.715	3.1	95	Phytosterol
		Stigmasterol	$C_{29}H_{48}O$	412	28.903	2.92	96	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.432	7.28	99	Phytosterol
	Neutral	Palmitic acid	$C_{16}H_{32}O_2$	256	22.539	2.4	99	Fatty acid
		Scopoletin	$C_{10}H_8O_4$	192	22.65	12.11	97	Coumarin
		1,9-Tetradecadiene	$C_{14}H_{26}$	194	23.08	1.65	98	Fatty acid
		Linoleic acid	$C_{18}H_{32}O_2$	280	23.474	0.58	98	Fatty acid
		Stearic acid	$C_{18}H_{36}O_2$	284	23.603	0.24	99	Fatty acid
		1-Hexacosene	$C_{26}H5_2$	364	24.88	1.14	90	Fatty acid
		Docosane	$C_{22}H_{46}$	310	25.568	0.28	97	n-Alkane
		Erucamide	$C_{22}H_{43}NO$	337	25.974	0.68	98	Fatty amide
		Vitamin E	$C_{29}H_{50}O_2$	430	27.774	0.42	93	Lipid-soluble compound
		Campesterol	$C_{28}H_{48}O$	400	28.703	2.4	99	Phytosterol
		Stigmasterol	$C_{29}H_{48}O$	412	28.897	2.14	99	Phytosterol
		γ-Sitosterol	$C_{29}H_{50}O$	414	29.432	5.69	99	Phytosterol

Conclusion

Foraging for wild edible plants is common among the indigenous people of developing countries. However, misidentification of poisonous plants for edible species can occur because of a lack of knowledge and experience. The present study showed that the ingestion of wild toxic Ipomoea, mistaken for edible *I. mauritiana*, resulted in food poisoning in the schoolchildren living in the rural area of Northeastern Thailand. Awareness of plant food safety is important to prevent food poisoning from wild plants.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Influence of low-dose X-ray on plasma membrane properties of erythroleukemia cell lines (K562, K562/adr)

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ABSTRACT

Background: Low-dose X-ray in medical use for diagnosis and therapy can result in cellular biology either directly or indirectly. In cell biology, the interaction of low-dose radiation generates many radical molecules that interact with cellular organelles, such as the plasma membrane.

Objectives: This study aimed to evaluate the effect of low-dose X-ray on both drug-sensitive (K562) and drug-resistant (K562/adr) erythroleukemic cell lines.

Materials and methods: Cells were exposed by using an X-ray at 135 kVp to obtain the absorbed dose of 0.05, 0.1, and 0.2 Gy. The intracellular reactive oxidant species (RS), malondialdehyde, membrane fluidity, drug uptake, and drug accumulation were instantly observed after radiation.

Results: The result showed a significant increase in RS in both cell lines as a function of radiation dose. In K562, the malondialdehyde (MDA) value increased in a radiation dose manner, while membrane fluidity was significantly modified at 0.1 and 0.2 Gy. In K562/adr, the uptake rate of pirarubicin (THP) and IC_{20} were altered but not significantly different from sham control.

Conclusion: Low-dose X-ray significantly increased the intracellular RS in both cell lines and decreased the membrane fluidity at 0.1 Gy of K562. There are alterations of anticancer drug uptake rate in both cell lines, but they are not significant.

Introduction

X-ray is classified as a low-linear energy transfer that is generally used for diagnosis and radiotherapeutic planning at a dose range of 0.0002-40 mGy.[1] However, it is still being used as low-dose radiation therapy (30-100 cGy) in regenerative medicine to increase cell proliferation and in pneumonia by suppressing inflammatory response.[2,3] Past studies on cellular effect have mostly focused on the degeneration of DNA. At low doses of X-ray, the studies showed the induction of DNA double-strand break.[4] In fact, the cellular effects of radiation are not selective. The cell membrane is the principal organelle that acts as a cell's boundary and is semipermeable for molecules. Certain substances can pass through the membrane depending on not only their properties but also the membrane's properties. When X-rays pass through the cell, the ionising radiation causes a breakout of molecules, and then free radicals such as reactive oxygen species (ROS)

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are generated. The consequential reaction of those molecules on unsaturated fatty acids, which is called lipid peroxidation, respectively provides products such as lipid hydroperoxides (LOOH), malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE). Those oxidative productions eventually lead to membrane fluidity alteration.[5,6]

Alteration of membrane fluidity relates to biological alteration in the sensitivity of drugs.[7] The previous observation of low-dose X-ray (up to 0.2 Gy of 120 kVp) on human peripheral blood mononuclear cells shows an augmentation of the intracellular ROS.[8] However, the instant effect of X-ray at 50, 70, and 100 kVp indicates an insignificant increase of osmotic fragility, and the alteration of membrane fluidity is observed at 4 hrs (100 kVp).[9] As mentioned, previous studies focus on normal haematopoietic cells but not on cancer cells. Moreover, the homogeneity of lipid composition between normal cells and cancer cells is different.[10] Hence, this study aimed to investigate the instant effect of low-dose X-ray on cancer cell membrane properties. Two erythroleukemic cell lines, drug-sensitive (K562) and drug-resistant (K562/adr), were exposed to low-dose X-ray up to 0.2 Gy.

Materials and methods

Chemicals

The 2',7'-Dichlorofluorescin diacetate (DCHF-DA; Sigma-Aldrich, USA) solution and 1,6-diphenyl-1,3,5-hexatriene (DPH, Sigma-Aldrich, Japan) were prepared at high concentration by solubilising them in DMSO and then diluting them till the appropriate concentration in phosphate buffer solution (PBS). The thiobarbituric acid reactive substances (TBARS) working reagent contained 2 mg/mL of 2-Thiobarbituric acid (Sigma-Aldrich, Japan), which is solubilised in a mixture of 50 mM NaOH (RCl Labscan, Thailand) and Glacial acetic acid (Fisher Scientific, UK) with a ratio of 1:1. Pirarubicin (THP, Sigma-Aldrich, Japan) was freshly prepared in DMSO, and then working solution (1 µM) was prepared in the physiological buffer (Luckoff-Na^+) of pH 7.3 that contained 132 mM NaCl, 3.5 mM KCl, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 20 mM HEPES, and 5 mM glucose. Then 0.1 mg/mL of resazurin sodium salt (Sigma-Aldrich, Japan) was sterilely prepared in PBS.

Cell lines

All experiments were performed on both drug-sensitive (K562) and drug-resistant (K562/adr) erythroleukemic cell lines. Cells were cultivated in a completed medium consisting of RPMI-1640 supplemented with 10% of foetal bovine serum and 1% penicillin-streptomycin for 72 hrs before experiments. The resistance property was maintained by cultivating with 400 nM of doxorubicin. For each experiment, cells were collected and exposed to the X-ray (135 kVp) at 0.05, 0.1, and 0.2 Gy. After irradiation, the intracellular RS, MDA, membrane fluidity, drug uptake, and cytotoxicity of the cells were immediately determined.

Determination of intracellular reactive oxidant species (RS)

Cells (5×10^5) were collected and resuspended in 0.1 mL phosphate buffer saline solution and then exposed to X-ray. After that, cells were added into a DCHF-DA solution (2 µM) and incubated for 30 min at 37 °C, 5% CO_2, and 95% humidity. The fluorescence intensity at 523 nm (excited at 502 nm) of dichlorofluorescin (F_{DCF}), which represented the RS level (mainly H_2O_2), was measured by a spectrofluorometer (Perkin Elmer, LS55, USA).[11,12]

Determination of lipid peroxidation

The TBARS assay was used to directly measure the MDA, which is a product of lipid peroxidation. Firstly, the cells ($4x10^6$) were incubated in the TBARS solution that consisted of 400 µL PBS and 500 µL of TBARS working reagent at 80 °C for 1 hour. Secondly, the solution was cooled down to 25 °C for 15 min, and then the sediment was discarded by centrifugation. Finally, the absorption spectrum of MDA-TBA reaction product was determined by spectrophotometer (Agilent, model 8453, China).[13,14] The MDA level was calculated from the MDA standard curve.

Determination of membrane fluidity

Membrane fluidity of the cell was determined by observing the accumulation of a fluorescence probe DPH that intercalated between lipid bilayers of the membrane. The fluorescence intensity of DPH (F_{DPH}) signified membrane fluidity.[9,15] Cells ($5x10^5$) were incubated in the 0.1 µM DPH solution (1,900 µL) for 10 min. Next, the fluorescence intensity (F_{DPH}) at 430 nm (excited at 350 nm) was determined by a spectrofluorometer at 37 °C.

Drug uptake

The cellular drug uptake assays were performed by using THP.[16] THP is an anticancer drug that passively diffuses across the plasma membrane by its lipophilicity property, and then the fluorescence intensity is quenched by DNA intercalation. The kinetic uptake of THP by cells ($2x10^6$) was performed at 37 °C by determining the fluorescence intensity of 1 µM of THP solution at 590 nm (excited at 480 nm). After cell addition, the fluorescence intensity was decreased by DNA intercalation that represents cellular drug uptake (uptake rate) across the plasma membrane. The uptake rate can be calculated from the slope of tangent by equation 1. The accumulation of the drug by cells (C_n) was calculated from the fluorescence intensity at a steady state (F_n) by equation 2 (Figure 1)

$$\text{Uptake rate} = \frac{\text{Slope}}{F_0} \times 1\mu M \quad (1)$$

$$C_n = \frac{F_0 - F_n}{F_0} \times 1\mu M \quad (2)$$

Cytotoxicity of pirarubicin

After irradiation, cells ($5x10^3$) were cultivated for 24 hrs in 96 wells/plate; each well contained 0.1 mL of the completed RPMI-1640 medium with the various concentrations of THP of 0-300 nM for K562 and 0-3000 nM for K562/adr. The living cells were determined by adding 0.01 mL of resazurin solution into each well and then incubating at 37 °C and humidifying with 5% CO_2 for 4 hrs. The fluorescence intensity at 590 nm was measured on a spectrofluorometer.[17] The cytotoxicity of THP was expressed as the inhibition concentration (IC) at 20% (IC_{20}). The IC value was calculated as follows.

$$IC = \frac{F_c - F_s}{F_c} \times 100 \quad (3)$$

Where F_s is the fluorescence intensity of irradiated cells, and F_c is the fluorescence intensity of control cells.

Statistical analysis

Statistical analysis was performed by OrigingPro8 Software. All data from independent experiments were described as mean±standard error (SE). All obtained parameters from a variety of radiation-absorbed doses were analysed by one-way ANOVA (Tukey procedure). Significance level was defined at the alpha value of 0.05.

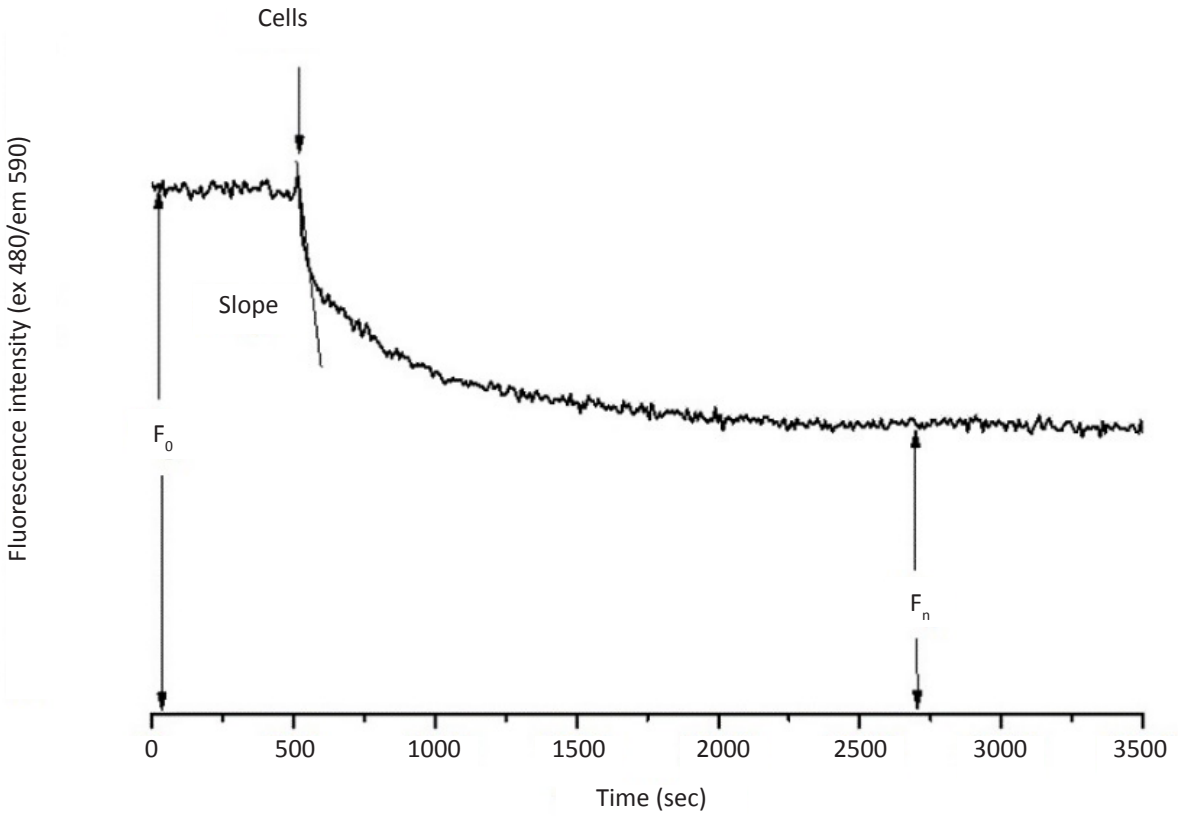


Figure 1. *Kinetic uptake of pirarubicin (THP) show the initial fluorescence intensity (F_0) of 1 µM of THP, slope (after adding cells), and the fluorescence intensity at steady state (F_n).*

Results

The effect of low-dose X-ray on cellular level was instantaneously investigated after irradiation. The fluorescence intensity of dichlorofluorescin (DCF) that represents the intracellular RS was determined. For sham control, the K562/adr cell line showed a fluorescence intensity of DCF lower than the K562 cell line. After irradiation, the RS level significantly increased in an absorbed dose-dependent manner either K562 or K562/adr. In this study, the lipid peroxidation production was evaluated from the MDA level. The MDA levels (mean±SE) of both non-irradiated K562 and K562/adr were equal to 2.12±0.16 and 3.27±0.17 fmole/cell, respectively. The MDA level in irradiated K562 was increased as a function of absorbed doses but not significantly different from non-irradiated K562; besides, no change of MDA level in irradiated K562/adr was detected. The result of membrane fluidity was determined by using the fluoresce probe DPH. Compared to the sham control, the fluorescence intensity of DPH of both irradiated cell lines slightly increased at a dose of 0.05, significantly increased at 0.1 Gy, and then decreased at 0.2 Gy (Figure 2).

Anticancer drug uptake and cytotoxicity

To evaluate the pharmacological properties of the membrane, the uptake rate of pirarubicin (THP) was used to indicate the passive diffusion of the drug across the plasma membrane. The kinetic uptake of THP, which is dependent on the membrane fluidity, was performed under the physiological buffer solution at 37 °C. In this condition, the result showed the drug uptake rate into the intact cells. In the sham control (0 Gy), the uptake rates of K562 and K562/adr are equal to 6.1±0.4 and 9.2±1.0 pM/sec, respectively. The uptake rate of irradiated cells is increased in the absorbed dose manner in both K562 and K562/adr cell lines, but not much differently from the sham control setting. The accumulation of THP (C_n) in both cell lines is calculated from the extinction of fluorescence intensity at a steady state. The C_n values of both irradiated cell lines were not different from the sham control. The C_n value of K562 is about 0.48-0.49 µM, but the value of K562/adr is about 0.22-0.25 µM. The cytotoxicity of THP was presented in term of IC_{20} values, which show the augmentation in K562/adr as 66.2±18.6, 84.3±17.3, 112.2±38.5, and 155.8±36.6 nM for 0, 0.05, 0.1,

and 0.2 Gy, respectively. In the case of K562, the IC_{20} values are 19.8±3.0, 23.3±6.1, 19.3±3.1, and 21.0±2.6 nM for 0, 0.05, 0.1, and 0.2 Gy, respectively (Figure 2). Finally, the mean±SE value of uptake rate, IC_{20}, and membrane fluidity were replotted in biplot as showed in Figure 3.

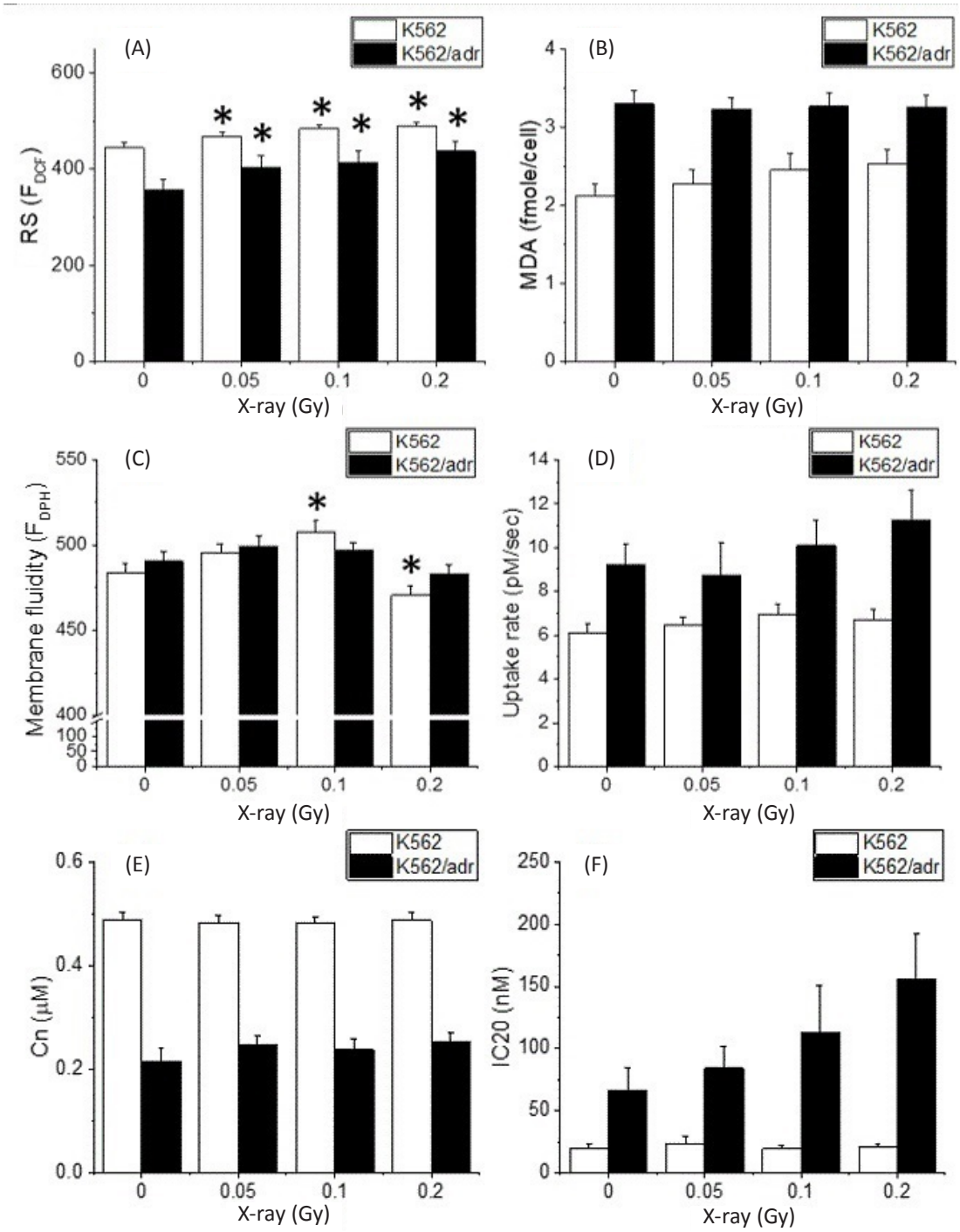


Figure 2. *Mean±SE value of Reactive oxidant species (RS). (A): MDA, (B): membrane fluidity, (C): uptake rate, (D): C_n (E) and IC_{20} of THP, (F) of K562 (□) and K562/adr (■) that exposed to X-ray at absorbed doses of 0, 0.05, 0.1 and 0.2 Gy (the asterisks represent the significantly different from 0 Gy at p<0.05).*

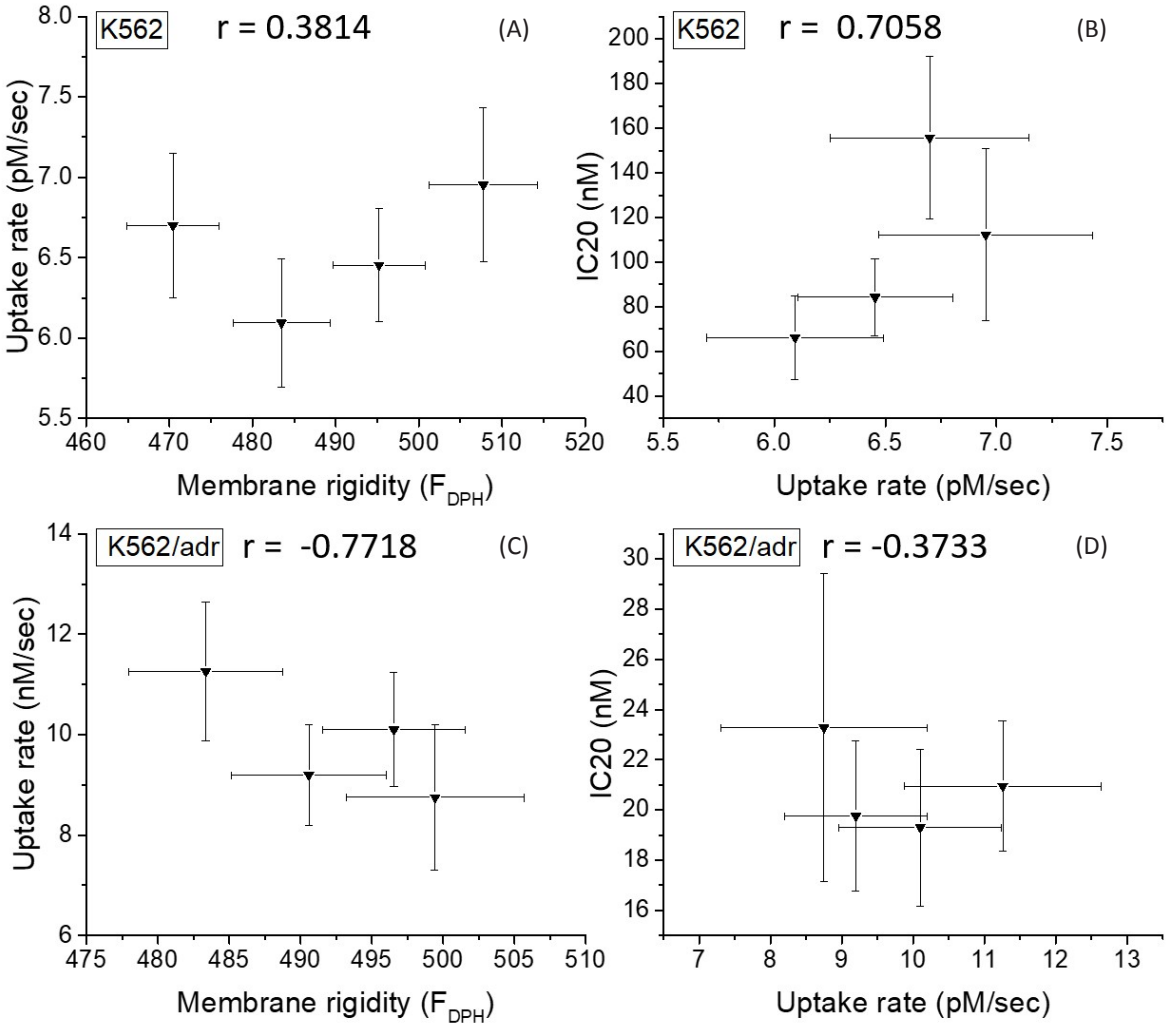
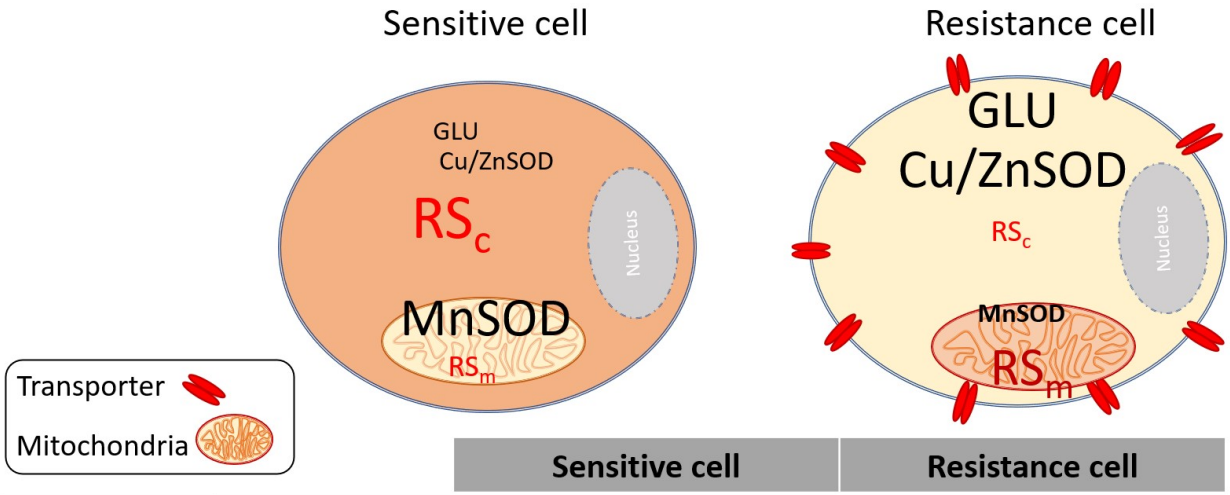


Figure 3. *Biplot (mean±SE) between uptake rate to membrane fluidity (A, C) and uptake rate to IC_{20} of THP (B, D) of K562 (Upper row) and K562/adr (Lower row), and the linear correlation coefficient (r).*

Discussion

Direct interaction of ionising radiation with matter generates free radical or oxidant species mainly in the form of ROS in a living cell. This leads to biological indirect effects such as lipid peroxidation, protein oxidation, and then DNA damage. In a resting state, the determined RS in drug-resistant cell line K562/adr are less than those of drug-sensitive cell line K562.[12] These values are the summation of RS, located in the mitochondria and cytoplasm. A previous study of cellular energetic state showed the mitochondrial membrane potential of K562 to be higher than K562/adr.[18] Therefore, this study supported that the free radical of the K562 cell is higher than K562/adr, which was generated from the mitochondria and then released in the cytoplasm. In the living cell, the intracellular superoxide dismutase plays an important role in cellular protection against RS. Two antioxidant enzymes, manganese superoxide dismutase (MnSOD) and copper/zinc superoxide dismutase (Cu/ZnSOD), respond to balance the oxidant radical at different locations in mitochondria and cytoplasm, respectively. Studies suggest that the MnSOD activity of K562 is higher than of K562/adr, while the Cu/ZnSOD activity of K562/adr is higher than of K562.[19] In this condition, the amount of cytoplasmic RS (RS_c) of K562 was more important than the amount of mitochondria RS (RS_m). Contrarily in K562/adr, the RS_m was more important than RS_c. Because of the different oxidative regulation in both cell lines, the data showed a higher degree of the MDA level of K562/adr than that of K562. Therefore, these lipid peroxidation productions probably result from RSm rather than RS_c.[20] According to the radiation cause on the increment of the oxidative state of K562 and K562/adr, the cellular response of both cell lines is not similar. Since mitochondria are considered critical organelles that induce cellular oxidative injuries by X-ray, several studies on these enzymes showed that the activity of MnSOD elevated, although Cu/ZnSOD was either reduced or induced by the effect of ionising radiation.[21-23] Other than those two enzymes, the cytosolic antioxidant such as glutathione (GSH) was found to be higher in K562/adr than in K562.[24] The study of GSH redox status also found it to be lessened by the effect of irradiation.[25] In our cases, it is possible that the radiation causes the elevation of RS in both cell lines, but the antioxidant defence systems in both cell lines are different. (Figure 4) These lead to the increase of MDA level in K562 but not

in K562/adr. Even if the MDA level elevation of K562 depends on the absorbed dose, the statistical test was insignificant when compared to the non-irradiation group. The membrane properties were assessed by observing the membrane fluidity and drug uptake. Fluidity of the membrane was determined by a DPH that interacts along the fatty acid path of the lipid membrane. The more fluorescence intensity means the less kinetic motion of the lipid bilayer, so the membrane becomes more rigid. In this study, the fluorescence of DPH of K562/adr was a bit higher than K562, which means that the membrane of K562/adr has less fluidity. These results were supported by the observation of a decrease in membrane fluidity and related with the degree of resistance.[26] The observation in both cell lines showed a biphasic response that is slightly decreased in membrane fluidity at 0.1 Gy and then increased at 0.2 Gy. Furthermore, the drug uptake basically depends on the membrane fluidity. The uptake rate of THP, which demonstrates the passive diffusion across the plasma membrane, did not show a significant modification. Moreover, the drug uptake rate did not show significant modification by the effect of ionising radiation. However, the biplots between uptake rate to membrane fluidity and uptake rate to IC_{20} of K562/adr illustrated a negative correlation.



		Sensitive cell	Resistance cell
Cytosol	MnSOD	Low	High
	Glutathione (GSH)	Low	High
	RS_c	High	Low
Mitochondria	MnSOD	High	Low
	RS_m	Low	High
Before radiation	Malondialdehyde (MDA)	Low	High
After radiation		Change	Not Change

Figure 4. *Model of oxidative balance in cytosol and mitochondria in sensitive and resistance cell: reactive oxidant species in cytosol (RS_c) and in mitochondria (RS_m) the antioxidant in mitochondria (MnSOD) and in cytosol (Cu/ZnSOD and glutathione (GSH)) and lipid peroxidation's product (malondialdehyde (MDA)).*

Conclusion

The findings of the K562 and K562/adr cell lines when exposed to low-dose X-ray of 135 kVp (up to 0.2 Gy) showed a significant increase in the intracellular RS, a mild increase in the MDA level in K562 but not in K562/adr, and a decrease of the membrane fluidity (0.1 Gy) and then increase at 0.2 Gy. The anticancer drug uptake rate in both cell lines is increased by the effect of radiation, but not significantly.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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Effect of Thai medicinal plants *Acanthus ebracteatus* Vahl. *Carthamus tinctorius* L. and *Streblus asper* Lour. on neurite outgrowth activity in Neuro-2A cells

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ABSTRACT

Background: Neurite outgrowth is an important process in neural reorganization and repair after neuronal injury. Neurite outgrowth is one of the important mechanisms to maintain normal physiological neuronal function. Neurite stimulation may help to prevent or rehabilitate brain regions in neurodegenerative disease.

Objectives: The aim of this study was to screen selected ethnopharmacological herbs for stimulatory effects on neurite outgrowth and to test for any cytotoxicity and phytochemical properties.

Materials and methods: The herbal extracts derived from *Acanthus ebracteatus* Vahl. leaves, *Carthamus tinctorius* L. flower, and *Streblus asper* Lour. bark was tested for neurite outgrowth stimulation/potentiation and cytotoxic and phytochemical properties.

Results: The extract of *Carthamus tinctorius* L. flowers at concentrations of 50 and 500 µg/mL could significantly stimulate potentiation of neurite outgrowth in Neuro-2a cells whereas other extracts could not. We found that treatment of the cells with a concentration up to 500 µg/mL of the *Carthamus tinctorius* L. extract showed no cytotoxicity.

Conclusion: The neurite potentiation effect might be due to other chemical constituents rather than phytochemical properties, especially total flavonoid, and phenolic contents, and antioxidant activity of the *Carthamus tinctorius* L. extract. The result showed that *Carthamus tinctorius* L. flowers extract could be a good candidate for use as a drug protecting against neuronal damage and neurodegenerative disease since it provides low cytotoxicity and neurogenic enhancement.

Introduction

In the past 20 years, there has been a significant productivity gap in the pharmaceutical industry.[1] This, in combination with the very high attrition rate, has been seen in the pharmaceutical industry, with many potential drugs not making it past initial trials.[2] It has been estimated that between 2000 and 2015, drugs developed for the nervous system had only a 15% chance of making it through Phase 1 trials.[3] Furthermore, the cost of drug development and the time required has skyrocketed in recent years, as it costs an estimated two to three billion US dollars and up to 12 years to bring a new chemical entity (NCE) to market.[4] This led many to search for new therapies for neurodegenerative diseases such as Parkinson's and Alzheimer's. Herbal medicines are one of the most used alternatives

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to conventional medicines,[5] and there is a vast number of drug-like NCEs produced by plants waiting to be identified and studied. Eighty percent of the world's population uses herbal remedies[6] and herbal medicines are particularly popular as memory enhancers.[7,8]

Better nutrition and health care mean people are living longer than at any time in the past. This change in demographic is occurring around the world as nations move faster from developing to developed. With this change comes an increased strain on health care systems as diseases related to age become more prevalent. The number of people living with AD is estimated to be 44 million people, and this is expected to rise to 135 million by 2050.[9] Neurite outgrowth is a critical event in neuronal pathfinding and the foundation of synaptic connections during development. Neurite outgrowth-enhancing compounds play an essential role in the restoration of the neural network which may result in preventing neurodegenerative disease. Many studies with herbal extracts have identified increased neurite outgrowth[10] as a potential feature of the herb's neuroprotective properties.[11,12] Thai medicinal herb *Streblus asper* Lour. (SA) Has previously been shown to protect against photoaging and provide neuroprotection in *C.elegans*.[13] *Acanthus ebracteatus* Vahl. (AE) has been shown to provide neuroprotective properties in the form of preventing oxidative stress caused by glutamate toxicity.[14,15] *Carthamus tinctorius* L. (CT) extracts have been shown to prevent excitotoxicity[16] and provide neuroprotection in rats and dogs.[17]

Therefore, the aim of this study was to screen these Thai medicinal herbs for neurite growth potentiating properties that may lend the herbs to potential use as treatments for neurodegenerative disease and use *in silico* technology to identify potential pathways that may be involved.

Materials and methods

Plant materials

SA and AE were obtained from the Princess Maha Chakri Sirindhorn Herbal Garden, Rayong Province. The samples were collected and identified by Professor Kasin Suvatabanghu, of Bangkok herbarium Thailand. The herbarium numbers for SA and AE are 013419 (BCU) and 013422 (BCU), respectively. The bark of SA and leaves of AE were extracted using maceration with 100% ethanol (avoiding water contamination and the need for a lyophilization step). Flowers of CT were kindly extracted and provided by Specialty natural products Co., Ltd., Chonburi Province.

Phytochemical analysis

Total flavonoid content

SA, AE, and CT were tested for their total flavonoid content using the Aluminium chloride colorimetric assay,[18] as previously described.[19] Briefly, in 96-well plates, rutin was used to generate a standard curve (100 µg/mL to 0.7 µg/mL). To each well, 5 µL of 10% aluminium chloride hexahydrate, 5 µL 1 M potassium acetate, and 140 µL of deionized water were incubated with 50 µL extract (0.5 to 5 mg/mL) and incubated for 40 min in the dark at room temperature. The absorbance at 415 nm was measured in a microplate reader. The total flavonoid content is represented as rutin equivalents (RE) mg/gm of dry extract.

Total phenolic content

SA, AE, and CT were tested for their total phenolic content using the Folin-Ciocateu method[20] as described previously.[21] Briefly, 50 µg of the extract (1 mg/mL) was mixed with 50 µL Folin-Ciocalteu phenol reagent. After 20 min, the mixture was neutralized by the addition of 50 µL of a 7.5% (w/v) Na_2CO_3 and incubated in the dark for 20 min at room temperature before the absorbance was measured at 760 nm. Gallic acid was used as a standard for the calibration curve. The total phenolic content was expressed as gallic acid equivalents (GAE/mg of plant extracts).

Total antioxidant scavenging activity

Total antioxidant scavenging activity was measured using the ABTS assay[22] as described previously.[23] Freshly prepared 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) ($ABTS^{\bullet+}$) (OD734=0.7-0.8) was diluted in ethanol. The extract (1 mg/mL) was mixed with $ABTS^{\bullet+}$ and incubated at room temperature for 30 min. Absorbance was measured at 517 nm and 734 nm, respectively. Trolox was used as the standard. The antioxidant capacity had Trolox equivalent antioxidant capacity (TEAC) in mg/gm of dry weight.

Cell Culture

Neuro-2a cells (Health Science Research Resources Bank (Osaka, Japan)) were cultured in a combination of DMEM and HAM's F-12 (50:50) with 10% FBS with penicillin/streptomycin. Cells were incubated at 37 °C in a humidified 5% CO_2 atmosphere. The cells were passed before reaching 8% confluency by briefly washing in PBS and incubating in trypsin-EDTA at 37 °C in a humidified 5% CO_2 atmosphere to lift the cells from the culture flask. The cells in trypsin-EDTA were diluted 1:1 in culture media and centrifuged at 500 *g* for 5 min. The Pellet was resuspended in culture media and cells plated for experiments or returned to a fresh culture flask.

Cell viability assay

Viable cells were quantified using the chemical [3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT), which was employed for assessing cell viability. Neuro-2a cells were plated at 5,000 cells per well in 96-well plates and allowed to adhere overnight in DMEM supplemented with 10% FBS. The following day, the serum was reduced to 1% and each plant extract was added. The cells were then incubated for 48 hrs. Then 5 mg/mL of MTT solution were added to the plate and allowed the MTT -formazan to develop for 4 hrs. The colorimetric reaction was measured at 550 nm. Half the maximal inhibition (IC_{50}) was calculated from three independent experiments using GraphPad Prism data analysis software (version 9 for Mac).

Neurite outgrowth assay

Neurite potentiation in Neuro-2a cells was carried out as previously described.[24] Neuro-2a cells were plated at 20,000 cells per well in 6-well plates and allowed to adhere overnight in DMEM supplemented with 10% FBS. The following day, the serum was reduced to 1% and each plant extract

was added. Cells were then incubated for 48 hrs at 37 °C before analysis under the light microscope. Cell numbers with neurite outgrowth-bearing cells and their neurite lengths were determined. Microscopic image acquisition at 20x was randomly selected in at least five different fields to analyze using image J.

All the data were analyzed with one-way ANOVA followed by Tukey's multiple comparison analysis using GraphPad Prism software (a $p<0.05$ was considered statistically significant).

Ultra-high performance liquid chromatography (UPLC)

Ultra-high performance liquid chromatography (UPLC) analysis of CT extract metabolic profiling: The analysis was carried out on a Thermo Exactive Orbitrap mass spectrometer coupled to Accela 600 (Thermo Fisher Scientific Inc) ultra-performance liquid chromatography (UPLC) pump and an Accela autosampler. Separation was carried out on a Kromasil C18 250 mm x 4.6 mm x 5 µm at 350 °C with a flow rate of 0.4 mL/min and an injection volume of 20 µL. Other conditions used: Ionization: Heated Electrospray (HESI); Transfer line temperature: 350 °C; Spray voltage: 4 kV; nebulizing gas: Nitrogen generated by Peak Scientific NM32LA model nitrogen generator. Analysis in positive mode was carried out in a gradient mobile phase with binary solvents containing Water with 0.1% formic acid as mobile phase A and Methanol with 0.1% formic acid as mobile phase B. The mobile phase B varied from 0-95% from 0-50 min, 95% B from 50-55 min, and initial conditions from 55.1-60 min. A similar program was used in negative ionization mode with mobile phase A as water and mobile phase B as acetonitrile.

Molecular formula of compounds was detected using HRMS by comparison of theoretical and observed mass. Compounds were identified from the previous literature on safflower.[25,26] Also by comparing the mass values with the existing databases like the knapsack family databases,[27] Metlin (http://metlin.scripps.edu), Lipidmaps, and the Dictionary of Natural Products.[28] Unidentified metabolites were then matched using other general chemical databases like Pubchem & Chemspider (http://pubchem.ncbi.nlm.nih.gov/; http://www.chemspider.com).

In silico analysis of CT extract was performed at the binding site of TrkB-D5 using Autodock 4.2 (The Scripps Research Institute, La Jolla, CA, USA)[29] and compared to 7,8-Dihydroxyflavone as a flavonoid compound that can enhance TrkB phosphorylation and promotes downstream cellular signaling.[30,31] TrkB crystal structure was obtained from the protein databank (http://www.pdb.org). All the ligand-protein interaction studies were using all the same conditions based on Chitranshi *et al*.[31]

Results

Phytochemical and antioxidant assay

We found that SA possesses the highest total flavonoid content. One gram of SA is equal to 83.163 mg of rutin. AE has the highest phenolic content and antioxidant activity. One gram of AE is equivalent to 679.75 mg of gallic acid and 277.98 mg of Trolox, respectively (Table 1).

Table 1 Phytochemical and antioxidant activity table of AE (sea holly), CT (safflower) and SA (tooth brush tree).

Herb (gm/mL)	Total flavonoid content	Total phenolic content	Total antioxidant activity
	mg of Rutin equivalent/gm extract weight of sample	mg of Gallic acid equivalent/ gm extract weight of sample (GAE)	mg of Trolox equivalent antioxidant /gm extract weight of sample (TEAC)
Acanthus ebracteatus Vahl.	64.653±23.410	679.759±9.308	277.986±38.308
Carthamus tinctorius L.	2.357±1.201	4.351±2.656	0.796±0.171
Streblus asper Lour.	83.163±2.068	146.719±1.817	48.276±2.735

Cell viability assay

MTT assays were used to evaluate and screen the toxicity of each herb (Figure 1). It was found that CT has the lowest toxicity (50% inhibitory concentration (IC_{50}) of more than 500 µg/mL) (Figure 1A). Whereas AE and SA have IC_{50} values in a similar range between 125 to 500 µg/mL (Figure 1B-1C). The IC_{50} values of the AE and SA are 201.47 and 195.44 µg/mL, respectively. Therefore, we selected a concentration range for CT of 5.5 to 500 µg/mL. Whereas the concentration range for AE and SA was 0.5, to 50 µg/mL.

Neurite count and neurite potentiation assay

We found that the CT can potentiate the length of the neurites at concentrations of 500 and 50 µg/mL in a statistically significant and dose-dependent manner. AE and SA had the opposite effect, resulting in statistically significant neurite length reduction at all concentrations (Figure 2A-2C). We also measured the percentage of cells that differentiated at each concentration; however, CT did not induce a greater percentage of cells to differentiate. Furthermore, AE and SA appeared to reduce the percentage of differentiated cells (Figure 2D-2F).

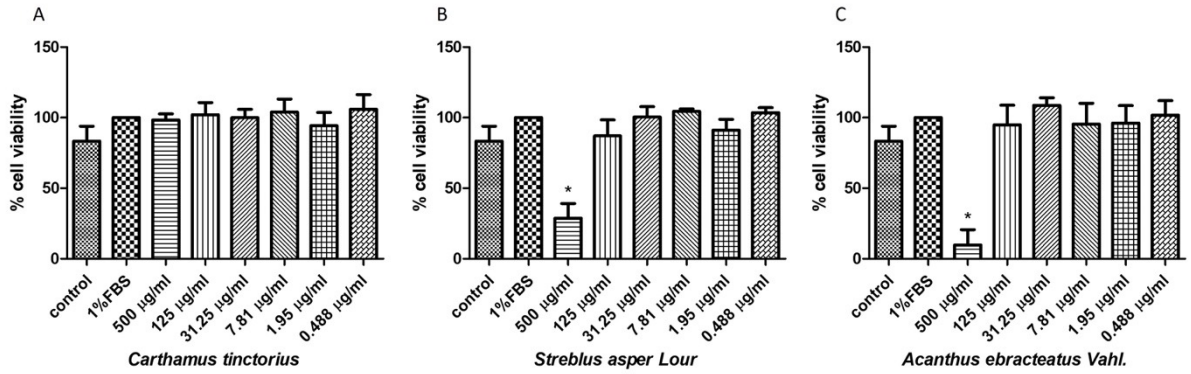


Figure 1. *Effects of Thai herbal extracts on cell viability, measured using the MTT assay. A: Carthamus tinctorius had no significant effect on cell viability effect up to 500 µg/mL, B: Streblus asper was not toxic at concentrations below 125 µg/mL, C: Acanthus ebracteaus was not toxic at concentrations below 125 µg/mL. *Statistical analysis using ANOVA followed by Tukey's post hoc test for significance compared to control p<0.05.*

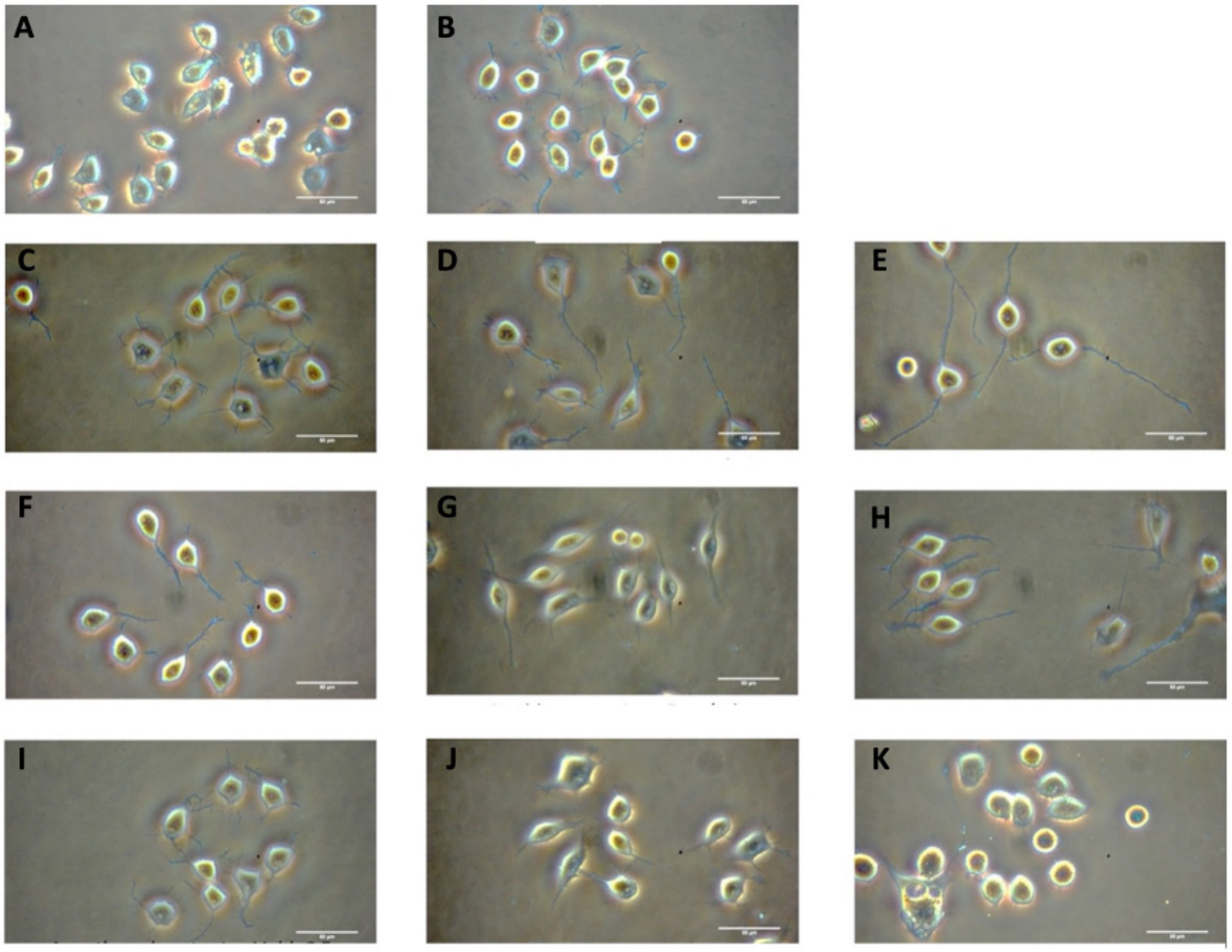


Figure 2. *Representative micrographs of N2A cells treated with A: control cells (untreated), B: control 1% FBS, C: 1% FBS + Carthamus tinctorius 5 µg/mL, D: 1% FBS + Carthamus tinctorius 50 µg/mL, E: 1% FBS + Carthamus tinctorius 500 µg/mL, F: 1% FBS + Streblus asper 0.5 µg/mL, G: 1% FBS + Streblus asper 5 µg/mL, H: 1% FBS + Streblus asper 50 µg/mL, I: 1% FBS + Acanthus ebracteatus 0.5 µg/mL, J: 1% FBS + Acanthus ebracteatus 5 µg/mL, K: 1% FBS + Acanthus ebracteatus 50 µg/mL.*

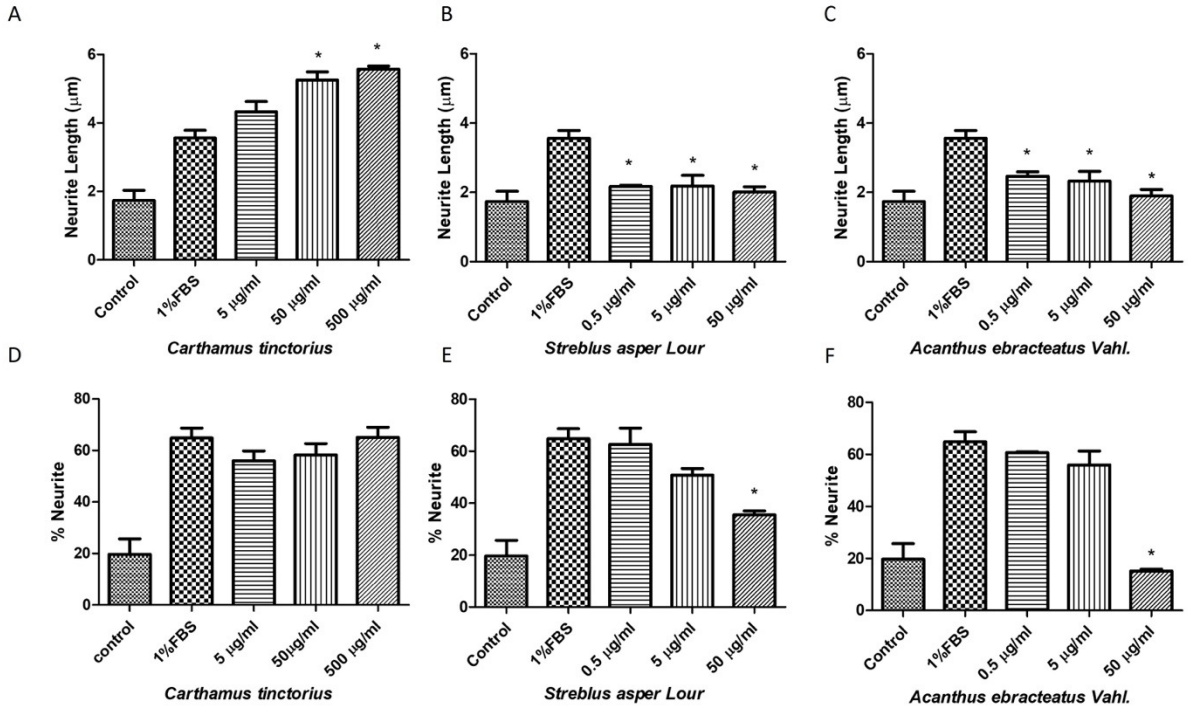


Figure 3. *Effect of Thai medicinal herbs on neurite outgrowth. A: potentiating effect of Carthamus tinctorius on the number of differentiated N2A cells in 1% FBS, B: Streblus asper failed to potentiate neurite outgrowth induced by 1% FBS and reduced the length of neurites, C: Acanthus ebracteatus failed to potentiate neurite outgrowth induced by 1% FBS and reduced the length of neurites, D: Carthamus tinctorius had no effect on the number of cells differentiated with neurites, E: Streblus asper reduced the number of cells with neurites back to the level of the control at 50 µg/mL, F: Acanthus ebracteatus reduced the number of cells with neurites back to the level of the control at 50 µg/mL. * Statistical analysis using ANOVA followed by Tukey's post hoc test for significance compared to 1% FBS p<0.05.*

Ultra-high performance liquid chromatography (UPLC)

The major compounds identified by UPLC-HRMS in safflower extract include flavonoids, Quinochalcones, and alkaloids. The UHPLC-HRMS chromatogram for CT extract is shown in Figure 4. Further studies are warranted on the isolation and characterization of the active principle(s) for a systematic study to identify new and potent drugs for therapeutical applications (Table 2).

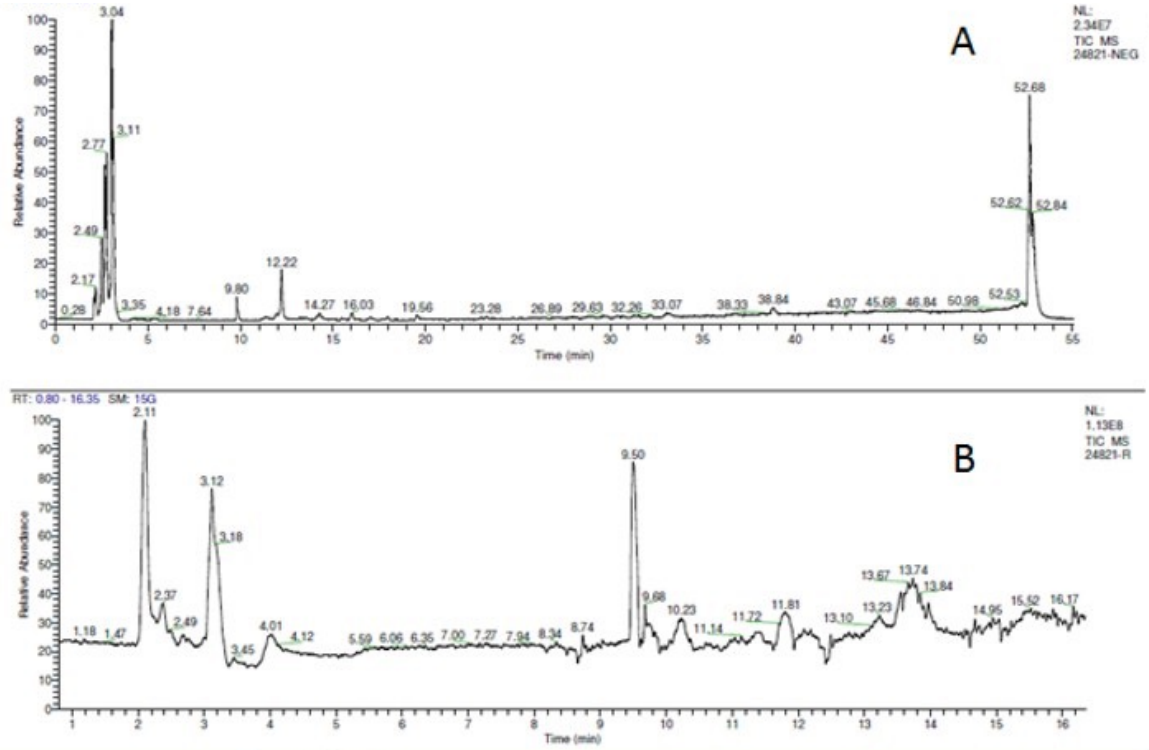


Figure 4. *Full scan UPLC-MS ESI spectrum of safflower extract. A: negative mode, B: positive mode.*

Although qualitative screening of CT chemical compounds has been reported previously by using different analytical techniques,[25,26] in the present study, we used the UPLC-HRMS approach, which facilitates the simultaneous detection of hundreds of compounds in an untargeted manner even if present in a low quantity.[32] The comprehensive data for the compounds in the crude extracts obtained using this approach can be useful for rational, prospective isolation, and identification of compounds of interest. Moreover, this approach is economical, saving valuable experimental time, typically required for fractionation, isolation, and purification.

Table 2 Putative identification of compounds from aqueous safflower extract, *Carthamus tinctorius* by UPLC-HRMS.

Sample No.	RT (min)	[M-H]- (m/z)		Formula [M-H]-	Identification
		Observed	Theoretical		
1	2.40-2.55	113.02349	113.02332	$C_5H_5O_3$	3-oxo-4-pentenoic acid
2	2.40-2.55	161.04492	161.04445	$C_6H_9O_5$	3-Hydroxymethylglutaric acid
3	2.40-2.55	191.05576	191.05501	$C_7H_{11}O_6$	Quinic acid
4	2.40-2.55	207.05079	207.05079	$C_7H_{11}O_7$	5- (3',4',dihydroxyphenyl) gamma valerolactone
5	2.40-2.55	221.06650	221.06558	$C_8H_{13}O_7$	Ethyl glucuronide 6-Acetyl-D-glucose
6	2.40-2.55	267.07274	267.07106	$C_9H_{15}O_9$	3-Deoxy-D-glycero-D-galacto-2-nonulosonic acid 2(α-D-Mannosyl)-D-glycerate
7	14.30	285.04169	285.03936	$C_{15}H_9O_6$	Kaempferol
8	23.19-23.32; 22.95-23.10	342.14684	342.14684	$C_{20}H_{22}O_5$	Unknown
9	14.36-14.50	363.12332	363.12270	$C_{22}H_{19}O_5$	3,6-Dimethoxy-6'',6''-dimethylpyrano [2,3:7,8]flavon
10	14.30	377.08751	377.08671	$C_{18}H_{17}O_9$	Unknown
11	22.95-23.10	381.01026	381.00885	$C_{15}H_9O_{12}$	Unknown
12	14.36	381.13386	381.13326	$C_{22}H_{21}O_6$	7,3'-Dihydroxy-5,4'-dimethoxy-5'-prenylisoflavone
13	3.08-3.18; 5.18-5.63	383.11984	383.11840	$C_{14}H_{23}O_{12}$	Acetyl-maltose (1-O-Acetyl-4-O-α-D-glucopyranosyl-α-D-glucopyranose)
14	12.12-12.27	385.09384	385.09179	$C_{20}H_{17}O_8$	5,6,7,8 Tetramethoxy3', 4'methylenedioxyisoflavone (Linderoflavone B)
15	11.22-11.47	396.11782	396.12035	$C_{22}H_{20}O_7$	Unknown
16	12.12-12.27	403.10432	403.10236	$C_{20}H_{19}O_9$	5,7Dihydroxy3,6,8,3', 4'pentamethoxyflavone
17	14.10-14.36	409.09057	409.09179	$C_{22}H_{17}O_8$	Epicatechin 3-O-p-hydroxybenzoate
18	11.22-11.47	435.09556	435.09806	$C_{13}H_{23}O_{16}$	Unknown
19	12.12-12.27	437.11000	437.10784	$C_{20}H_{21}O_{11}$	Loquatoside
20	14.10-14.36	447.09540	447.09219	$C_{21}H_{19}O_{11}$	Carthamone
21	14.30	447.09545	447.09806	$C_{14}H_{23}O_{16}$	Unknown
22	5.18-5.63	447.31018	447.31050	$C_{27}H_{43}O_5$	Agigenin
23	14.36; 14.36-14.50	449.11068	449.10784	$C_{21}H_{21}O_{11}$	Carthamidin 5-glucoside
24	11.22-11.47	461.07484	461.07733	$C_{14}H_{21}O_{17}$	Unknown
25	23.19-23.32; 22.95-23.10	462.20501	462.20369	$C_{28}H_{30}O_6$	Unknown
26	12.12-12.27	473.10978	473.10784	$C_{23}H_{21}O_{11}$	Kaempferol 3-(4''-acetylrhamnoside)
27	12.12-12.27	491.12060	491.11840	$C_{23}H_{23}O_{12}$	Quercetin 3,3'-dimethyl ether 7-glucoside
28	11.22-11.47	491.12161	491.12428	$C_{16}H_{27}O_{17}$	Unknown
29	3.08-3.18; 5.18-5.63	499.16731	499.16575	$C_{19}H_{31}O_{15}$	3-{[6-O-(D-Galactopyranosyl)-β-D-galactopyranosyl] oxy}-1,2-propanediyl diacetate
30	14.10-14.36; 14.30	503.17958	503.17592	$C_{22}H_{31}O_{13}$	(S)-Multifidol 2-[apiosyl-(1->6)-glucoside]
31	15.88-16.19	514.13713	514.13758	$C_{15}H_{30}O_{19}$	Unknown
32	14.36	518.13252	518.13600	$C_{32}H_{22}O_7$	Unknown
33	14.21	525.17912	525.18140	$C_{21}H_{33}O_{15}$	Unknown
34	5.18-5.63	531.33140	531.33163	$C_{31}H_{47}O_7$	1α,25-dihydroxy-22-oxavitamin D3 3-hemiglutarate
35	12.12-12.27; 12.09-12.33	539.14154	539.13953	$C_{24}H_{27}O_{14}$	Unknown
36	22.95-23.10	545.01716	545.01981	$C_{23}H_{13}O_{16}$	Unknown
37	22.95-23.10; 23.19-23.32	545.01716	582.26708	$C_{29}H_{42}O_{12}$	Unknown
38	11.22-11.47	545.17547	545.17123	$C_{20}H_{33}O_{17}$	Unknown
39	14.21	557.09747	557.09845	$C_{19}H_{25}O_{19}$	Unknown

Table 2 Putative identification of compounds from aqueous safflower extract, *Carthamus tinctorius* by UPLC-HRMS. (continued)

Sample No.	RT (min)	[M-H]- (m/z)		Formula [M-H]-	Identification
		Observed	Theoretical		
40	16.90-17.15	573.25776	573.25417	$C_{27}H_{41}O_{13}$	Unknown
41	15.88-16.19	574.15899	574.16222	$C_{35}H_{26}O_{8}$	Unknown
42	14.54-14.74	577.15878	577.16105	$C_{20}H_{33}O_{19}$	Unknown
43	23.19-23.32	582.26287	545.01981	$C_{23}H_{13}O_{16}$	Unknown
44	14.21; 14.54-14.74; 14.36-14.50; 15.41-15.59	591.26805	591.26473	$C_{27}H_{43}O_{14}$	10,12,14-Aromadendranetriol
45	15.88-16.19; 15.70-15.83	592.16960	592.17278	$C_{35}H_{28}O_{9}$	Unknown
46	12.09-12.33	593.15279	593.15010	$C_{27}H_{31}O_{16}$	Unknown
47	16.90-17.15	593.15345	593.15010	$C_{27}H_{29}O_{15}$	Safflor yellow A
48	11.22-11.47	595.14638	595.14462	$C_{30}H_{27}O_{13}$	(2S)-5,7,3',4'-Tetrahydroxyflavanone 7-(6-p-coumaroyl-glucoside)
49	5.18-5.63	596.18978	596.18883	$C_{31}H_{32}O_{12}$	Unknown
50	14.54-14.74; 15.70-15.83; 15.41-15.59	609.14880	609.14501	$C_{27}H_{29}O_{16}$	Rutin
51	15.88-16.19	609.15806	609.16027	$C_{31}H_{29}O_{13}$	4'-O-Methylcarthamidin 7-(2-p-coumaroylglucoside)
52	12.09-12.33; 14.36	611.16285	611.16066	$C_{27}H_{31}O_{16}$	Hydroxysafflor yellow A
53	19.45-19.67	621.00636	621.00885	$C_{35}H_{9}O_{12}$	Unknown
54	14.21	623.12790	623.12428	$C_{27}H_{27}O_{17}$	Kaempferol 3-glucuronide-7-glucoside
55	16.90-17.15	623.16476	623.16066	$C_{28}H_{31}O_{16}$	Quercetin 3,4'-dimethyl ether 7-alpha-L-Arabinofurano-syl-(1->6)-glucoside
56	14.54-14.74; 14.30; 14.10-14.36	625.14346	625.13993	$C_{27}H_{29}O_{17}$	6-hydroxykaempferol 3,6-diglucoside
57	11.83-11.92	625.14356	625.14344	$C_{45}H_{21}O_{4}$	Unknown
58	15.88-16.19	628.14509	628.14227	$C_{3028}O_{15}$	Unknown
59	19.45-19.67	636.98058	636.98264	$C_{38}H_{5}O_{11}$	Unknown
60	15.70-15.83	637.14415	637.13993	$C_{28}H_{29}O_{17}$	Kaempferol 3-glycosides
61	12.09-12.33	639.12238	639.11919	$C_{27}H_{27}O_{18}$	Quercetin 3-glucosyl-(1->2)-glucuronide
62	14.21	645.11011	645.10863	$C_{29}H_{25}O_{17}$	-O-p-Coumaryoylglucose; β-D-form, 3'-Hydroxy, 3,4-bis(3,4,5-trihydroxybenzoyl)
63	15.41-15.59	647.14222	647.13953	$C_{33}H_{27}O_{14}$	Acremonidin
64	19.45-19.67	653.34387	653.34141	$C_{48}H_{45}O_{2}$	Unknown
65	14.54-14.74	664.19049	664.18453	$C_{27}H_{36}O_{19}$	Unknown
	15.88-16.19; 15.41-15.59; 15.70-15.83	669.20628	669.20253	$C_{30}H_{37}O_{17}$	Unknown
66	19.45-19.67	671.20145	671.20292	$C_{26}H_{39}O_{20}$	Unknown
67	14.36-14.50	673.27245	673.27021	$C_{31}H_{45}O_{16}$	Unknown
68	19.45-19.67	677.50045	677.49870	$C_{40}H69O_{8}$	Unknown
69	14.10-14.36; 14.21	683.14873	683.14540	$C_{29}H_{31}O_{19}$	Unknown
70	11.83-11.92	685.20091	685.20095	$C_{48}H_{29}O_{5}$	Unknown
71	19.45-19.67	689.30404	689.30404	$C_{50}H_{41}O_{3}$	Unknown
72	15.41-15.59; 15.70-15.83	691.15255	691.15049	$C_{31}H_{31}O_{18}$	3,5-di-O-(beta-Glucopyranosyl) pelargonidin 6''-O-4, 6'''-O-1-cyclic malate
73	12.09-12.33	693.16669	693.18727	$C_{28}H_{37}O_{20}$	Unknown
74	14.36	693.16929	693.16614	$C_{31}H_{33}O_{18}$	3,5-di-O-(β-Glucopyranosyl) pelargonidin 6''-O-4, 6'''-O-1-cyclic malate
75	14.54-14.74	697.16463	697.16105	$C_{30}H_{33}O_{19}$	Tricetin 3'-methyl ether 7,5'-diglucuronide Malvidin 3-glucoside-5-(6-acetylglucoside)
76	15.88-16.19	712.12052	712.12702	$C_{33}H_{28}O_{18}$	Unknown
77	14.30	757.22591	757.21857	$C_{33}H_{41}O_{20}$	Chalconaringenin 2'-O-glucoside 4'-O-gentobioside

Table 2 Putative identification of compounds from aqueous safflower extract, *Carthamus tinctorius* by UPLC-HRMS. (continued)

Sample No.	RT (min)	[M-H]- (m/z)		Formula [M-H]-	Identification
		Observed	Theoretical		
78	11.83-11.92	801.17588	801.18140	$C_{44}H_{33}O_{15}$	Unknown
79	11.83-11.92	855.09397	855.09806	$C_{48}H_{23}O_{16}$	Unknown
80	11.83-11.92	949.25121	949.25496	$C_{50}H_{45}O_{19}$	Unknown

***In silico* analysis**

Protein-ligand analysis of TrkB protein showed the binding affinity with safflor yellowA (-12.83 kcal/mol) <<Rutin (-5.45 kcal/mol) <7,8-dihydroxyflavone (-5.39 kcal/mol) <Kaemferol (-5.14 kcal/mol) <Carthamone (-4.95 kcal/mol) <Carthamidin (-4.8 kcal/mol) <Hydroxysafflor yellow (-3.99 kcal/mol) from the strongest through the weakest, respectively.

The results from Table 3 and Table 4 show the binding affinity of TrkB receptor and the phytochemical compounds. TrkB-domain5 (TrkB-D5) structures were subjected to binding with compounds and compared with the standard 7, 8-dihydroxyflavone, which is considered an agonist of TrkB receptor.[31]

Table 3 Docking results of tropomyosin receptor kinase B (TrkB) receptor and their ligands.

Compound	Binding energy (kcal/mol)	ki	Distance	Bond
7,8-dihydroxyflavone	-5.39	112.08 uM	1.94894	Conventional H-bond
			1.78703	Conventional H-bond
			2.3485	Conventional H-bond
			2.616	C-H bond
			2.6452	Pi-Donor H-bond
			4.44823	Pi-Pi Stacked
			4.31386	Pi-Pi Stacked
Hydroxysafflor yellow A	-3.99	1.2 mM	2.60402	Conventional H-bond
			2.58561	Conventional H-bond
			2.30369	Conventional H-bond
			1.72765	Conventional H-bond
			2.04315	Conventional H-Bond
			1.81622	Conventional H-bond
			1.97012	Conventional H-bond
			1.75147	Conventional H-bond
			2.78871	Conventional H-bond
			1.80168	Conventional H-Bond
			2.14573	Conventional H-Bond
			3.64398	Pi-Pi Stacked
Safflor yellow A	-12.83	394.2 pM	1.68362	Conventional H-bond
			2.19582	Conventional H-bond
			2.07502	Conventional H-bond
			1.89083	Conventional H-bond
			2.70312	Conventional H-bond
			2.7302	Conventional H-bond
			2.70956	Conventional H-bond
			2.50703	Conventional H-bond
			2.84909	Conventional H-bond
			2.79666	Conventional H-bond
			2.96361	Conventional H-bond
			3.45809	Pi-Donor H-bond
			3.81576	Pi-Donor H-bond

Table 3 Docking results of tropomyosin receptor kinase B (TrkB) receptor and their ligands. (continued)

Compound	Binding energy (kcal/mol)	ki	Distance	Bond
Carthamidin 5-glucoside	-4.8	302.04 uM	3.03833	Conventional H-bond
			2.12193	Conventional H-bond
			1.80641	Conventional H-bond
			2.21713	Conventional H-bond
			1.80319	Conventional H-bond
			2.34617	Conventional H-bond
			1.63428	Conventional H-bond
			1.94458	Conventional H-bond
			3.53715	Pi-Anion
			3.03298	Pi-Donor H-bond
Carthamone	-4.95	235.69 uM	2.06727	Conventional H-bond
			1.86897	Conventional H-bond
			1.84223	Conventional H-bond
			2.54015	Conventional H-bond
			2.55252	Conventional H-bond
			2.3009	Conventional H-bond
			1.84095	Conventional H-bond
			5.57327	Pi-Sulfur
Kaempferol	-5.14	172.17 uM	1.72218	Conventional H-bond
			1.81133	Conventional H-bond
			2.99255	Pi-Donor H-bond
			2.77906	Pi-Lone Pair
			5.0164	Pi-Pi T-shaped
			5.39479	Pi-Alkyl
			5.4388	Pi-Alkyl
			4.44785	Pi-Alkyl
Rutin	-5.45	101.61 uM	1.79658	Conventional H-bond
			2.27913	Conventional H-bond
			2.04409	Conventional H-bond
			1.82278	Conventional H-bond
			1.77808	Conventional H-bond
			2.01204	Conventional H-bond
			2.02454	Conventional H-bond
			2.31962	Conventional H-bond
			3.09527	Conventional H-bond
			3.5869	C-H Bond
			4.10904	Pi-Anion
			2.31515	Pi-Donor H-bond
			4.67722	Alkyl
			5.23425	Pi-Alkyl
			4.02085	Pi-Alkyl

Table 4 Molecular docking interaction between safflower compound and 7,8-dihydroxyflavone.

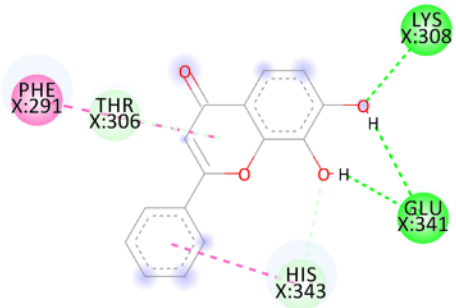
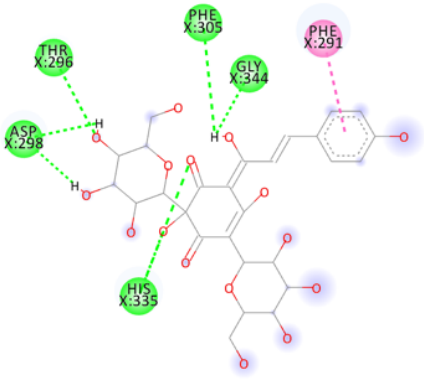
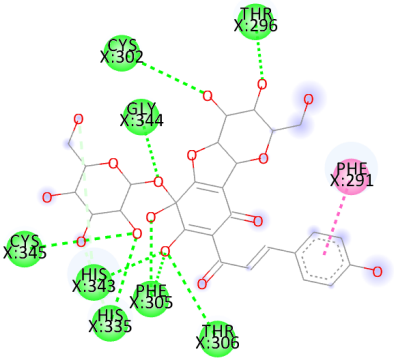
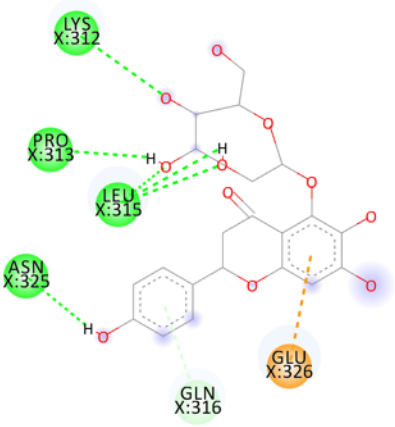
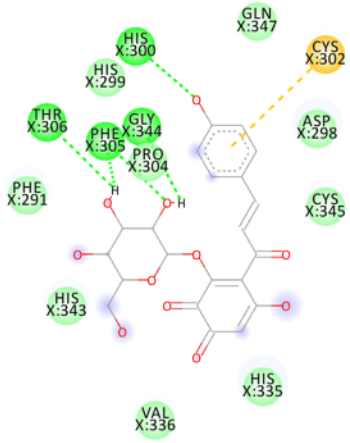
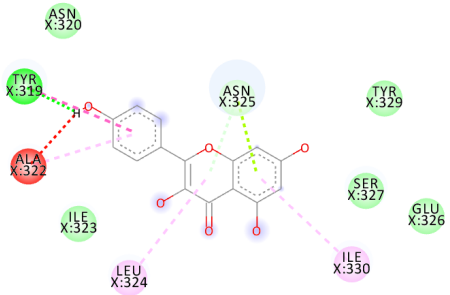
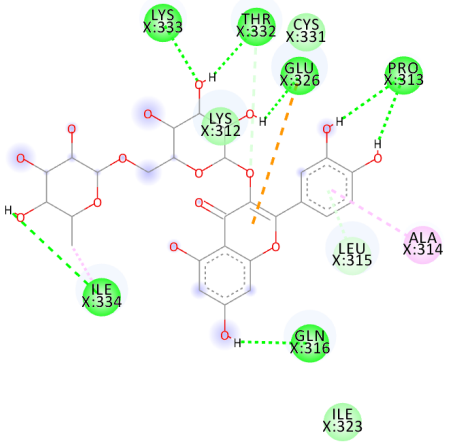
Compound	Ligand-Protein interaction
7,8-dihydroxyflavone	
Hydroxysafflor yellow A	
Safflor yellow A	
Carthamidin 5-glucoside	

Table 4 Molecular docking interaction between safflower compound and 7,8-dihydroxyflavone. (continued)

Compound	Ligand-Protein interaction
Carthamone	
Kaempferol	
Rutin	

Discussion

In this study, we have investigated the extracts of AE, SA, and CT, and we found them to be relatively non-toxic (within the ranges tested), with CT showing no toxicity at any of the concentrations we tested. In the neurite outgrowth analysis, it was CT that was able to potentiate the growth of neurites (an important event in neuronal pathfinding and the foundation of synaptic connections during development). AE and SA were not effective, in inducing neurite outgrowth, and even reduced the number of neurite-producing cells, possibly due to their higher toxicity levels. Interestingly CT has the lowest flavonoid, phenolic and antioxidant activity out of all three extracts.

Following CT's potentiation of neurite outgrowth, we sort to investigate possible compounds and pathways that may be involved. We made use of UHPLC-HRMS identifying 80 separate compounds. We selected the following compounds for *in silico* analysis safflor yellowA, Rutin, 7,8-dihydroxyflavone, Kaemferol, Carthamone, Carthamidin, and Hydroxysafflor yellow based on previous studies suggesting these compounds

may be active in the TrkB pathway, which is involved in neurite development.[33]

TrkB receptor plays an important role in neuronal plasticity and is involved in many neurodegenerative diseases. TrkB receptor is regulated the cell survival, migration, outgrowth of axons and dendrites, synaptogenesis, synaptic transmission, and synaptic remodeling. Activation of TrkB can result in therapeutic in neurodegenerative disease.[33] Even though natural TrkB agonists such as Brain-derived neurotrophic factor (BDNF) have been suggested that it can be beneficial for Parkinson's,[35] Alzheimer's,[36] and glutamate-induced cytotoxicity,[37] the recombinant BDNF has not given satisfactory therapeutic results due to their short half-life and problems with delivery.[38, 39] Therefore, searching for a small molecule that mimics BDNF activity may represent a beneficial therapeutic agent against a variety of human disorders. Several previous studies have linked safflower and its phytochemical compounds to the BDNF/TrkB/ERK pathway.[33,40-41] These studies, as well as our *in-silico* findings suggest that the BDNF/TrkB/ERK pathway is the cause of the neurite outgrowth effects seen in N2A cells treated with SA extracts.

Conclusion

Our findings suggest that CT extracted could be a functional food or food supplement. CT has been used for a long time in the traditional medical treatment for rheumatism and paralysis,[42] has anti-bacterial and anti-fungal properties.[43] It is important to note that even though the phenolic, flavonoid and antioxidant activity of CT extracted is less than other compounds but showed significantly enhanced neurite outgrowth in a dose-dependent manner. Some of the safflower compounds are possibly related to cell survival and plasticity through the TrkB signaling pathway. Interestingly the safflor yellow A, a compound found in *Carthamus tinctorius* L. extract, showed a protective effect in cardiomyocytes against anoxia/reoxygenation in vitro.[44] However, there is a study suggesting that safflower oil supplements in rats can change memory and learning and increase neuronal growth cone and some of the neurotransmitters in the brain.[45] Based on our findings, we believe further research into the neuroprotective and neurite-inducing properties of these herbs is warranted.

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Psychometric properties of the Vocal Fatigue Index – Thai Version

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ABSTRACT

Background: Voice disorders can be found in many scenarios. Many people have experienced vocal problems in their lifetime. Such problems can occur occasionally or permanently during the course of life. Previous literature review showed that vocal fatigue usually occurs concurrently with voice disorders, though it could occur alone as well. Vocal fatigue is considered the first symptom of a vocal problem and usually improves after voice rest. Detecting vocal fatigue before an individual develops a voice disorder is extremely important.

Objectives: This study aims to 1) translate the original VFI into the Thai version and 2) evaluate the psychometric properties of VFI-TH, including content validity, face validity, predictive validity (sensitivity and specificity), and reliability.

Materials and methods: Participants in this study consisted of two groups comprising one group of 22 participants with voice disorders and another group of 60 participants with healthy voices. The age of participants was 18 years and older.

Procedures: Cross-cultural protocol of translation was followed per Beaton, which consisted of five steps: Initial translation, synthesis of the translation, back translation, expert committee review, and pretesting. This study was divided into 2 phases. Phase I consisted of the first three steps of Beaton's guideline, while Phase II was the evaluation of psychometric properties; content validity by expert committee review, face validity by data trial in ten participants with voice disorders, predictive validity through sensitivity and specificity by formula calculation, and reliability were examined by evaluating internal consistency through Cronbach's Alpha co-efficiency.

Results: The results showed that the VFI-TH had content validity, face validity, and predictive validity. For predictive validity, the percentages of sensitivity and specificity were 22.7 and 100, respectively, and internal consistency was 0.87-0.94, which meant very good or excellent.

Conclusion: The VFI-TH had content validity, specificity, and reliability to detect vocal fatigue. However, the VFI-TH should be used along with other vocal assessments in adults aged 18 years and older.

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Introduction

Voice disorders can occur among professionals who use their voices often, such as teachers, singers, actors, lawyers, salespeople, and non-occupational voice users.[1,2] Most disorders are caused by using the voice for a long time, using inappropriate pitch and loudness, shouting, as well as screaming, and talking at a high pitch. These kinds of manipulations of voice use can lead to temporary or permanent voice problems that affect daily lives.[3] The American Speech-Language-Hearing Association (ASHA) defines voice disorders as those that occur when voice quality, pitch, and loudness differ or are inappropriate for an individual's age, gender, cultural background, or geographic location.[4-6] Voice disorders also appear when an individual expresses concern about having an abnormal voice that does not meet daily needs, even if others do not perceive it as different or deviant.[7-10] Common symptoms include aphonia, hoarseness, harshness, muscle strain, and vocal fatigue. Vocal fatigue is regarded as the first sign of a voice disorder.

There is no definition for vocal fatigue in the Classification Manual for Voice Disorders-I.[11] On the other hand, many symptoms indicate vocal fatigue, such as excessive effort while speaking, tiredness, voice loss during speaking, and worsening vocal quality.[12] Indications of vocal fatigue may not be detected by direct endoscopic examination of the larynx.[3,13] Per literature, in consensus, vocal fatigue is defined as a quantifiable decline in function (performance or perceptual) that influences vocal task performance and is individual-specific.[12] At present, the measurement of vocal fatigue mostly involves using individual self-reported questionnaires, among which the most widely accepted and used is the Vocal Fatigue Index.[14]

The Vocal Fatigue Index, or VFI, is a questionnaire that was developed by Nanjundeswaran in 2015.[14] The VFI consists of nineteen questions divided into three parts. Part 1 is related to the tiredness of the voice and avoidance of voice use. Part 2 is related to physical discomfort, while part 3 is related to improving symptoms with rest. This test utilizes a Likert scale score from 0-4, and each part is interpreted independently. The original VFI has different cut-off scores for each part. The cut-off score for part 1 is ≥24, while for part 2 it is ≥7, and for part 3 it is ≤7. Individuals with vocal fatigue should meet the criteria for both parts 1 and 3. The VFI has been translated into many languages including Portuguese,[15] German,[16] Indian,[17,18] Persian,[19] Turkish,[20] Hong Kong-Chinese,[21] Croatian,[22] Korean,[23] Japanese,[24] etc.

In Thailand, Speech-Language Pathologists (SLPs) have limited available voice assessment tools, and none of them are specific for the evaluation of vocal fatigue. Accordingly, Thai SLPs provided with the VFI Thai version would be able to use it as a tool for early detection of vocal fatigue before individuals develop other problems due to voice disorders. It could be helpful for therapists to diagnose and prevent voice problems among individuals who seek voice therapy at an early stage.

Materials and methods

This study consisted of two phases: 1) translation and cross-cultural adaptation of the VFI following Beaton's guidelines[25] and 2) psychometric properties evaluation of the VFI-TH. The VFI developer accepted the author's request for permission to translate on July 16th, 2018. The study was approved by the Research Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University (Approval ID: AMSEC-61EX-098) and the Ethics Committee on Researches Involving Human Subjects Rajavithi Hospital (EC number: 090/2019).

Participants

There were two groups of participants: Twenty-two participants with voice disorders and sixty with healthy voices.

1. Voice disorders group

The inclusion criteria were age over 18 years old, and the ability to speak and read in Thai. Participants had to have presented with voice disorders in the last six months with the frequency of voice problems most or all of the time, have symptoms of laborious speaking, and/or the ability of pronunciation increased, and/or changing of vocal quality, and diagnosed with voice disorders with benign lesions by an otolaryngologist. The exclusion criteria included having psychiatric and/or neurological diseases that could affect understanding the questionnaire, using/getting psychiatric medication, and inability to do the questionnaire by themselves.

2. Normal voice group

The inclusion criteria were; age over 18 years old, the ability to speak and read in Thai, and the absence of voice problems in the last six months. If any voice issues had occurred in the previous six months, the frequency and duration of the problems must have been less than two weeks.

Procedures

Phase 1: Translation and cross-cultural adaptation of the VFI

In this process, the focus was on translation across cultures, for which the author followed Beaton's Guidelines.[25] The guidelines suggest five stages when translated in a cross-culture setting: Initial translation, synthesis of the translation, back translation, expert committee review, and pretesting. The last two stages are shown in the second phase. The steps and details for the first phase of this study are as follows:

1.1 Initial translation

The first step was forward translation using two expert translators with independent backgrounds who were unfamiliar with the VFI. The first translator (T1) was an otolaryngologist knowledgeable in voice disorders. T1 translated the original into VFI-T1. The second translator (T2) was a linguistics professor who translated into VFI-T2.

1.2 Synthesis of the translation

The two translators (T1 and T2) and the first two authors synthesized the results of translations (VFT-T1 and VFI-T2) to produce one synthesized translation (VFI-T12).

1.3 Back translation

Another two independent translators who were experts in the English and Thai languages translated VFI-T12 from Thai into English. This step had VFI-BT1 and VFI-BT2.

Phase 2: Psychometric properties evaluation of the VFI-TH

This part consisted of four evaluation steps. The first two steps involved the procedure in Beaton's guidelines, including expert committee review and pretesting, which are also called content validity and face validity, respectively. Subsequently, predictive validity was carried out through the assessment of sensitivity and specificity of the VFI-TH and reliability.

I. Validity

2.1 Expert committee review

An expert committee review is also called an evaluation of content validity. The conference of the expert committee was set for May 31st, 2019. There were two Speech-Language Pathologists (SLPs) who were experienced in voice disorders and one laryngologist who specialized in laryngeal problems. The meeting between experts involved reviewing content, making equivalent cross-cultural outputs, and editing differences found according to the opinion of the experts. This step produced the VFI-expert version.

2.2 Pretesting

The last stage of the cross-cultural protocol was pretesting. The trial applied the VFI-expert version to ten participants who had voice disorders with benign lesions. Interpreting vocal fatigue results and collecting comments and/or the part that should be fixed were done after participants completed the index by the first author. The VFI-expert version was adjusted through face validity and proofreading, then getting the VFI-TH version.

2.3 Predictive validity through sensitivity and specificity

Sensitivity is the ability of a test to correctly identify patients with vocal fatigue (True Positive) and individuals with voice disorders.[26-28] Specificity is the ability of a test to correctly identify people without vocal fatigue (True Negative) and individuals with no voice disorders.[28,29] It is used to confirm a screening test's ability and differentiate between individuals who have vocal fatigue and those who do not.[28] Table 1 shows sensitivity and specificity by comparing the standard test and the VFI-TH.

Table 1 Determination of sensitivity and specificity.[28, 29]

The VFI-TH	Standard test	
	Voice disorders	No voice disorders
Vocal fatigue	a (True Positive)	b (False Positive)
No vocal fatigue	c (False Negative)	d (True Negative)
	Sensitivity=$\frac{a}{(a+c)}$	Specificity=$\frac{d}{(b+d)}$

II. Reliability

Reliability for this study analyzed the internal consistency for each part of the VFI-TH and total items using Cronbach's Alpha co-efficiency.

Results

The demographic data for all participants are shown in Tables 2 and 3.

Table 2 Demographic information for 22 voice disorder participants.

	n	(%)		n	(%)
1. General information			**2. Voice problems**		
Gender			**Voice problems in the last six months**		
Male	11	(50)	Yes	22	(100)
Female	11	(50)	No	0	(0)
Age			**Frequency**		
18-29	2	(9.1)	Sometime	9	(41)
30-39	5	(22.7)	Most of the time	5	(23)
40-49	2	(9.1)	Always	8	(36)
50-59	4	(18.2)	**Duration (weeks)**		
≥60	9	(40.9)	<2	4	(18)
Level of education			≥2	18	(82)
< Bachelor's degree	8	(36.4)	**Voice therapy**		
Bachelor's degree	11	(50)	Yes	10	(45.5)
Master's degree	3	(13.6)	No	12	(54.5)
> Master's degree	0	(0)	**3. Medical information**		
Occupation			**Lesion**		
Teacher/professor	1	(4.55)	Structural		
Religious leader	1	(4.55)	Vocal nodules	4	(18.2)
Farmer	2	(9.1)	Vocal polyps	2	(9.1)
Merchant	3	(13.6)	Vocal edema	1	(4.5)

Table 2 Demographic information for 22 voice disorder participants. (continued)

	n	(%)		n	(%)
Etc.	15	(68.2)	Granuloma	2	(9.1)
Engineer	1	-	Neurological		
Journalist	1	-	TVC paralysis	13	(59.1)
Nurse	1	-	Vocal tremor	0	(0)
Dietitian	1	-	Bowing cord	0	(0)
Office worker	1	-	Spasmodic dysphonia	0	(0)
Writer	1	-	Underlying diseases		
Retired government officer	2	-	Diabetes mellitus	1	-
Government officer	2	-	Hypertension	1	-
Lawyer	1	-	Laryngopharyngeal reflux	6	-
No work	3	-	Deny underlying diseases	10	-
Job involves continuous voice use			Etc.		
Yes	11	(50)	Heart disease	2	-
No	11	(50)	Allergic rhinitis	3	-
Average voice use in a day (hours)			Thyroid	1	-
<1	1	(9.1)	Dyslipidemia	1	-
1-3	7	(63.6)			
4-6	3	(27.3)			
>6	0	(0)			

Table 3 Demographic information for 60 typical participants.

	n	(%)		n	(%)
1. General information			**1. General Information (cont.)**		
Gender			**Job involves continuous voice use**		
Male	20	(33.3)	Yes	41	(68.3)
Female	40	(66.7)	No	19	(31.7)
Age			**Average voice use in a day (hours)**		
18-29	11	(18.3)	<1	0	(0)
30-39	32	(53.3)	1-3	18	(43.9)
40-49	8	(13.3)	4-6	12	(29.3)
50-59	2	(3.3)	>6	11	(26.8)
≥60	7	(11.8)	**2. Voice problems**		
Level of education			**Voice problems in the last six months**		
< Bachelor's degree	6	(10)	Yes	11	(18.3)
Bachelor's degree	27	(45)	No	49	(81.7)
Master's degree	18	(30)	**Frequency**		
> Master's degree	9	(15)	Sometime	11	(100)
Occupation			Most of the time	0	(0)
Teacher/professor	10	(16.7)	Always	0	(0)
Religious leader	1	(1.7)	**Duration (weeks)**		
Merchant	4	(6.6)	<2	11	(100)
Student	1	(1.7)	≥2	0	(0)
Salesman	6	(10)	**Voice therapy**		
Interpreter/guide	2	(3.3)	Yes	0	(0)
Technician	1	(1.7)	No	11	(100)

Table 3 Demographic information for 60 typical participants. (continued)

	n	(%)		n	(%)
Etc.	35	(58.3)	**3. Medical information**		
Office worker	13	-	**Underlying diseases**		
Retired	3	-	Diabetes mellitus	1	-
Nurse	5	-	Hypertension	2	-
Doctor	2	-	Laryngopharyngeal reflux	1	-
Administrator	2	-	Deny underlying diseases	50	-
Audiologist	2	-	Etc.		
Psychologist	1	-	Allergic rhinitis	6	-
Dietarian	1	-	Thyroid	1	-
Journalist	1	-			
Speech-language pathologist	1	-			
Government officer	1	-			
Freelance consultant	1	-			
Self-employed	1	-			
Accountant	1	-			

Validity

Validity in this study was analyzed by 1) content validity through expert committee review, 2) face validity through pretesting or trial, and 3) predictive validity through calculating sensitivity and specificity.

1. Content validity

In the meeting, editing of the context was carried out for cultural adaptation in some questions and adding descriptions to provide additional information to increase understanding. Examples include item no.5 "It feels like work..." no.12 "pain in the neck", and no.15 "throat aches", as shown in Figure 1 and Figure 2. Explanations were added such as "having voice disorders involves focusing on using the voice like at work when compared with a normal voice that is speaking natural", "pain on the muscle of the neck", and "when using voice, it is a sudden pain", respectively. Experts held discussions until they formed a consensus and got the VFI-expert version.

Part 1					
1. I don't feel like talking after a period of voice use	0	1	2	3	4
2. My voice feels tired when I talk more	0	1	2	3	4
3. I experience increased sense of effort with talking	0	1	2	3	4
4. My voice gets hoarse with voice use	0	1	2	3	4
5. It feels like work to use my voice	0	1	2	3	4
6. I tend to generally limit my talking after a period of voice use	0	1	2	3	4
7. I avoid social situations when I know I have to talk more	0	1	2	3	4
8. I feel I cannot talk to my family after a workday	0	1	2	3	4
9. It is effortful to produce my voice after a period of voice use	0	1	2	3	4
10. I find it difficult to project my voice with voice use	0	1	2	3	4
11. My voice feels weak after a period of voice use	0	1	2	3	4
Part 2					
12. I experience pain in the neck at the end of the day with voice use	0	1	2	3	4
13. I experience throat pain at the end of the day with voice use	0	1	2	3	4
14. My voice feels sore when I talk more	0	1	2	3	4
15. My throat aches with voice use	0	1	2	3	4
16. I experience discomfort in my neck with voice use	0	1	2	3	4
Part 3					
17. My voice feels better after I have rested	0	1	2	3	4
18. The effort to produce my voice decreases with rest	0	1	2	3	4
19. The hoarseness of my voice gets better with rest	0	1	2	3	4

These are some symptoms usually associated with voice problems. Circle the response that indicates how frequently you experience the same symptoms (0-never, 1-almost never, 2-sometimes, 3-almost always, and 4-always).

Figure 1. The Vocal Fatigue Index-Original (VFI).[14]

รหัส

แบบประเมินดัชนีวัดการล้าของเสียงฉบับภาษาไทย

(Vocal Fatigue Index – Thai Version)

คำแนะนำ อาการเหล่านี้มักสัมพันธ์กับปัญหาของเสียง
ให้ท่านวงกลมล้อมรอบคำตอบ ที่บ่งชี้ว่าท่านประสบกับอาการแบบเดียวกันบ่อยเพียงไร

คะแนน
- 0 **หมายถึง** **ไม่เคย** (อาการดังกล่าวไม่เคยปรากฏขึ้น)
- 1 **หมายถึง** **แทบไม่เคย** (อาการดังกล่าวปรากฏขึ้นน้อยครั้ง แต่ละครั้งปรากฏขึ้นห่างกัน)
- 2 **หมายถึง** **บางครั้ง** (อาการดังกล่าวปรากฏขึ้นนานๆครั้ง แต่ปรากฏบ่อยครั้งมากขึ้น)
- 3 **หมายถึง** **เกือบตลอดเวลา** (อาการดังกล่าวปรากฏขึ้นเกือบตลอดเวลา)
- 4 **หมายถึง** **ตลอดเวลา** (อาการดังกล่าวปรากฏขึ้นตลอดเวลา)

	ตอนที่ 1	**ไม่เคย**	**แทบไม่เคย**	**บางครั้ง**	**เกือบตลอดเวลา**	**ตลอดเวลา**
1	ข้าพเจ้ารู้สึกไม่อยากพูดคุยหลังจากการใช้เสียงมาระยะเวลาหนึ่ง	0	1	2	3	4
2	ข้าพเจ้ารู้สึกเหนื่อยเมื่อพูดมากขึ้น	0	1	2	3	4
3	ข้าพเจ้าต้องออกแรงมากขึ้นในขณะพูด	0	1	2	3	4
4	ข้าพเจ้ามีอาการเสียงแหบเมื่อใช้เสียง	0	1	2	3	4
5	ข้าพเจ้ารู้สึกเหมือนทำงานขณะใช้เสียง	0	1	2	3	4
6	ข้าพเจ้ามีแนวโน้มที่จะจำกัดการพูดคุยภายหลังจากการใช้เสียงมาระยะเวลาหนึ่ง	0	1	2	3	4
7	ข้าพเจ้าหลีกเลี่ยงสถานการณ์ทางสังคมเมื่อรู้ว่าข้าพเจ้าต้องพูดคุยมากขึ้น	0	1	2	3	4
8	ข้าพเจ้ารู้สึกว่าไม่สามารถพูดคุยกับครอบครัวหลังจากทำงานมาทั้งวัน	0	1	2	3	4
9	ข้าพเจ้าต้องออกแรงเปล่งเสียงมากภายหลังจากการใช้เสียงมาระยะเวลาหนึ่ง	0	1	2	3	4

Figure 2. *The Vocal Fatigue Index-Thai Version (VFI-TH).*

10	ข้าพเจ้าพบว่ามีความยากลำบากในการเปล่งเสียง	0	1	2	3	4
11	ข้าพเจ้าพูดเสียงเบาลงเมื่อใช้เสียงมาระยะเวลาหนึ่ง	0	1	2	3	4
	คะแนนรวม					

หมายเหตุ

"รู้สึกเหมือนทำงาน" หมายถึง เมื่อมีปัญหาเสียงผิดปกติ ต้องฝืนใช้เสียงเหมือนทำงาน แต่เมื่อเทียบกับการไม่มีปัญหาเสียง การพูดนั้นจะเป็นไปตามธรรมชาติ

ตอนที่ 2		**ไม่เคย**	**แทบไม่เคย**	**บางครั้ง**	**เกือบตลอดเวลา**	**ตลอดเวลา**
12	ข้าพเจ้ารู้สึกปวดกล้ามเนื้อคอเมื่อสิ้นสุดวันที่มีการใช้เสียง	0	1	2	3	4
13	ข้าพเจ้ารู้สึกเจ็บในลำคอเมื่อสิ้นสุดวันที่มีการใช้เสียง	0	1	2	3	4
14	ข้าพเจ้ารู้สึกเจ็บ/แสบคอเมื่อพูดคุยมากขึ้น	0	1	2	3	4
15	ข้าพเจ้าปวดในลำคอเมื่อใช้เสียง	0	1	2	3	4
16	ข้าพเจ้าไม่สบายคอเมื่อมีการใช้เสียง	0	1	2	3	4
	คะแนนรวม					

หมายเหตุ

"ปวดกล้ามเนื้อคอ" หมายถึง ปวดกล้ามเนื้อภายนอกคอ

"ปวดในลำคอเมื่อใช้เสียง" หมายถึง เมื่อมีการใช้เสียง รู้สึกปวดในลำคอทันที

ตอนที่ 3		**ไม่เคย**	**แทบไม่เคย**	**บางครั้ง**	**เกือบตลอดเวลา**	**ตลอดเวลา**
17	ข้าพเจ้ารู้สึกเสียงดีขึ้นหลังจากได้พัก	0	1	2	3	4
18	ข้าพเจ้าใช้แรงในการออกเสียงลดลงเมื่อได้พัก	0	1	2	3	4
19	อาการเสียงแหบของข้าพเจ้าลดลงเมื่อได้พัก	0	1	2	3	4
	คะแนนรวม					

Figure 2. *The Vocal Fatigue Index-Thai Version (VFI-TH). (continued)*

2. Face validity

Modification was done both in the general record form and the VFI-TH. Externally in record form (Figures 3 and 4), each question item and Likert score were highlighted for precise and easy understanding, and a description of the score and word tabs in the score headline was added. A trial conducted on participants found that 4 of 10 participants offered feedback that most of the comments and suggestions needed further explanation.

หน้า 1 ของ 2 หน้า

หน้า 1

แบบบันทึกข้อมูลกลุ่มเสียงผิดปกติ

สำหรับการศึกษาแบบประเมินดัชนีวัดการล้าของเสียงฉบับภาษาไทย

วันที่			**รหัส**
ส่วนที่ 1 : ข้อมูลส่วนตัว			
1. เพศ	☐ ชาย	☐ หญิง	
2. อายุ	☐ 18-29 ปี	☐ 30-39 ปี	☐ 40-49 ปี
	☐ 50-59 ปี	☐ ตั้งแต่ 60 ปีขึ้นไป	
3. ระดับการศึกษา	☐ น้อยกว่าปริญญาตรี	☐ ปริญญาตรี	☐ ปริญญาโท
4. อาชีพ	☐ นักเรียน/นักศึกษา	☐ ครู/อาจารย์	☐ นักร้อง/นักแสดง
	☐ พนักงานขาย	☐ ล่าม/มัคคุเทศก์	☐ พระ/ผู้นำศาสนา
	☐ ค้าขาย	☐ เกษตรกร	☐ ช่าง
	☐ พนักงานขับรถ	☐ พนักงานทำความสะอาด	
	☐ ทำอาหาร	☐ พนักงานรักษาความปลอดภัย	
	☐ ระบุ		
5. งานของท่านมีการใช้เสียงต่อเนื่องหรือไม่		☐ มี	☐ ไม่มี (***ข้ามไปทำส่วนที่ 2)***
6. จำนวนชั่วโมงเฉลี่ยที่ใช้เสียงต่อเนื่องใน 1 วัน		☐ น้อยกว่า 1 ชั่วโมง	☐ 1-3 ชั่วโมง
		☐ 4-6 ชั่วโมง	☐ มากกว่า 6 ชั่วโมง
ส่วนที่ 2 : ปัญหาเสียงผิดปกติ			
1. ในช่วง 6 เดือนที่ผ่านมา		☐ มี	☐ ไม่มี ***(ข้ามไปทำข้อ 4)***
2. ความถี่ของปัญหาเสียง		☐ นาน ๆ ครั้ง	☐ เป็นส่วนมาก
		☐ ตลอดเวลา	
3. ระยะเวลาของปัญหาเสียง		☐ น้อยกว่า 2 สัปดาห์	☐ 2 สัปดาห์ ขึ้นไป
4. เคยได้รับการฝึกเสียงมาก่อนหรือไม่		☐ เคย	☐ ไม่เคย

ฉบับที่ 3 วันที่ 4 มีนาคม 2563

Figure 3. *General record form for voice disorder participants.*

*** สำหรับผู้วิจัย เป็นผู้กรอกข้อมูล ***

หน้า 2

รหัส				
ส่วนที่ 3: (สำหรับผู้วิจัย) ข้อมูลทางการแพทย์				
Lesion	Organic voice disorders Structural: ☐ Vocal nodule (Rt/Lt) ☐ Vocal polyp (Rt/Lt) ☐ Edema (Rt/Lt) ☐ Granuloma ☐ ..... Neurological: ☐ TVC paralysis (Rt/Lt) ☐ Vocal tremor ☐ Bowing cord (Rt/Lt) ☐ Spasmodic dysphonia ☐			
U/D	☐ Diabetes Mellitus (DM) ☐ Hypertension (HT) ☐ Laryngopharyngeal Reflux (LPR) ☐			
VFI	**Factors**		**VF score**	**Cut-off score**
	Factor: 1*	Tiredness of voice and voice avoidance		**≥ 24**
	Factor: 2	Physical discomfort associated with voicing		≥ 7
	Factor: 3*	Improvement of symptoms with rest		**≤ 7**
	Vocal fatigue (factor 1,3) ☐ Yes ☐ No			

Figure 3. *General record form for voice disorder participants. (continued)*

หน้า 1

แบบบันทึกข้อมูลกลุ่มเสียงปกติ

สำหรับการศึกษาแบบประเมินดัชนีวัดการล้าของเสียงฉบับภาษาไทย

วันที่			**รหัส**
ส่วนที่ 1 : ข้อมูลส่วนตัว			
1. เพศ	☐ ชาย	☐ หญิง	
2. อายุ	☐ 18-29 ปี	☐ 30-39 ปี	☐ 40-49 ปี
	☐ 50-59 ปี	☐ ตั้งแต่ 60 ปีขึ้นไป	
3. ระดับการศึกษา	☐ น้อยกว่าปริญญาตรี	☐ ปริญญาตรี	☐ ปริญญาโท
4. อาชีพ	☐ นักเรียน/นักศึกษา	☐ ครู/อาจารย์	☐ นักร้อง/นักแสดง
	☐ พนักงานขาย	☐ ล่าม/มัคคุเทศก์	☐ พระ/ผู้นำศาสนา
	☐ ค้าขาย	☐ เกษตรกร	☐ ช่าง
	☐ พนักงานขับรถ	☐ พนักงานทำความสะอาด	
	☐ ทำอาหาร	☐ พนักงานรักษาความปลอดภัย	
	☐ ระบุ		
5. งานของท่านมีการใช้เสียงต่อเนื่องหรือไม่		☐ มี	☐ ไม่มี (***ข้ามไปทำส่วนที่ 2)***
6. จำนวนชั่วโมงเฉลี่ยที่ใช้เสียงต่อเนื่องใน 1 วัน		☐ น้อยกว่า 1 ชั่วโมง	☐ 1-3 ชั่วโมง
		☐ 4-6 ชั่วโมง	☐ มากกว่า 6 ชั่วโมง
ส่วนที่ 2 : ปัญหาเสียงผิดปกติ			
1. ในช่วง 6 เดือนที่ผ่านมา		☐ มี	☐ ไม่มี ***(ข้ามไปทำข้อ 4)***
2. ความถี่ของปัญหาเสียง		☐ นาน ๆ ครั้ง	☐ เป็นส่วนมาก
		☐ ตลอดเวลา	
3. ระยะเวลาของปัญหาเสียง		☐ น้อยกว่า 2 สัปดาห์	☐ 2 สัปดาห์ ขึ้นไป
4. เคยได้รับการฝึกเสียงมาก่อนหรือไม่		☐ เคย	☐ ไม่เคย

Figure 4. *General record form for typical participants.*

หน้า 2 ของ 2 หน้า

*** สำหรับผู้วิจัย เป็นผู้กรอกข้อมูล ***

หน้า 2

รหัส				
ส่วนที่ 3: (สำหรับผู้วิจัย) ข้อมูลทางการแพทย์				
U/D	☐ Diabetes Mellitus (DM) ☐ Hypertension (HT) ☐ Laryngopharyngeal Reflux (LPR) ☐			
VFI	Factors		VF score	Cut-off score
	Factor: 1*	Tiredness of voice and voice avoidance		**≥ 24**
	Factor: 2	Physical discomfort associated with voicing		≥ 7
	Factor: 3*	Improvement of symptoms with rest		**≤ 7**
	Vocal fatigue (factor 1,3) ☐ Yes ☐ No			

Figure 4. *General record form for typical participants. (continued)*

3. Predictive validity

Sensitivity was calculated for twenty-two individuals who were diagnosed with voice disorders. It was found that only five participants had vocal fatigue because they met the criteria for parts 1 and 3, while seventeen participants had no vocal fatigue, as shown in Table 4. Participants with vocal fatigue divided by total participants in the voice disorders group were calculated as the sensitivity of the VFI-TH, which was 22.7 percent (Table 5).

Table 4 Details of the VFI-TH parts 1 and 3 in the voice disorders group (n=22).

Participants	VFI-TH		Criteria meet cut-off	Vocal fatigue
	Part 1 ≥24	Part 3 ≤7		
RV01	29	6	Part 1,3	Yes
RV02	14	0	Part 3	No
RV03	2	0	Part 3	No
RV04	5	12	None	No
RV05	24	10	Part 1	No
RV06	15	9	None	No
RV07	24	10	Part 1	No
RV08	26	5	Part 1,3	Yes
RV09	22	12	None	No
RV10	30	6	Part 1,3	Yes
RV11	26	10	Part 1	No
RV12	19	2	Part 3	No
RV13	13	6	Part 3	No
RV14	9	3	Part 3	No
RV15	40	9	Part 1	No
RV16	42	0	Part 1,3	Yes
RV17	12	6	Part 3	No
RV18	25	8	Part 1	No
RV19	30	6	Part 1,3	Yes
RV20	23	9	None	No
RV21	17	6	Part 3	No
RV22	5	4	Part 3	No
Meet criteria	**10**	**13**	**None=4**	**Yes=5**
Range	**2-42**	**0-12**		

Table 5 Cross tabulation between the VFI-TH and the reference standard.

Cross tabulation		Reference standard		Total
		Yes	No	
VFI-TH	Yes	5 (22.7%)	0 (0%)	5
	No	17 (77.3%)	60 (100%)	77
Total		22	60	82

Specificity was calculated in the same way as sensitivity. For this study, it was calculated for sixty individuals with normal voices. It was found that none of the participants had vocal fatigue. The results showed that participants who had no voice disorders also had no concurrent vocal fatigue, as shown in Table 6, because none of the participants met the criteria for parts 1 and 3. Therefore, the ability of the VFI-TH to discriminate against individuals with no vocal fatigue in a normal voice was calculated as 100 percent (Table 5).

Table 6 Details of the VFI-TH parts 1 and 3 in the typical group (n=60).

Participants	VFI-TH		Criteria meet cut-off	Vocal Fatigue	Participants	VFI-TH		Criteria meet cut-off	Vocal fatigue
	Part 1 ≥24	Part 3 ≤7				Part 1 ≥24	Part 3 ≤7		
RN01	10	12	None	No	RN31	4	6	Part 3	No
RN02	9	12	None	No	RN32	2	0	Part 3	No
RN03	5	1	Part 3	No	RN33	14	10	None	No
RN04	0	0	Part 3	No	RN34	19	5	Part 3	No
RN05	29	8	Part 1	No	RN35	9	1	Part 3	No
RN06	17	9	None	No	RN36	23	10	None	No
RN07	33	10	Part 1	No	RN37	22	9	None	No
RN08	15	8	None	No	RN38	0	8	None	No
RN09	19	12	None	No	RN39	4	11	None	No
RN10	0	1	Part 3	No	RN40	2	0	Part 3	No
RN11	6	1	Part 3	No	RN41	26	11	Part 1	No
RN12	14	6	Part 3	No	RN42	10	6	Part 3	No
RN13	12	10	None	No	RN43	9	10	None	No
RN14	7	12	None	No	RN44	23	8	None	No
RN15	13	2	Part 3	No	RN45	6	10	None	No
RN16	13	4	Part 3	No	RN46	18	5	Part 3	No
RN17	7	5	Part 3	No	RN47	1	0	Part 3	No
RN18	13	10	None	No	RN48	0	0	Part 3	No
RN19	18	11	None	No	RN49	3	2	Part 3	No
RN20	5	12	None	No	RN50	2	9	None	No
RN21	0	0	Part 3	No	RN51	0	0	Part 3	No
RN22	0	0	Part 3	No	RN52	16	12	None	No
RN23	6	3	Part 3	No	RN53	8	3	Part 3	No
RN24	5	0	Part 3	No	RN54	2	5	Part 3	No
RN25	8	6	Part 3	No	RN55	8	6	Part 3	No
RN26	10	4	Part 3	No	RN56	27	9	Part 1	No
RN27	12	9	None	No	RN57	29	9	Part 1	No
RN28	17	12	None	No	RN58	11	6	Part 3	No
RN29	18	12	None	No	RN59	26	12	Part 1	No
RN30	25	11	Part 1	No	RN60	4	6	Part 3	No
Meet criteria Range		**Part 1 = 7 Part 1 =0-33**		**Part 3 = 30 Part 3 = 0-12**		**None = 23**		**Vocal Fatigue**	**Yes = 0**

Reliability

This study collected data on the same day participants consented to join the study. Reliability was assessed through SPSS (version 28) to analyze internal consistency using Cronbach's Alpha coefficient within a 95% confidence interval. The results showed that VFI-TH parts 1, 2, 3, and total items were .93, .87, .94, and .94, respectively.

Table7 Internal consistency of the VFI-TH (n=82).

VFI-TH	No. of items	Cronbach's α coefficient
Part 1	11	0.93
Part 2	5	0.87
Part 3	3	0.94
Total	19	0.94

**95% confidence interval*

Discussion

Validity

Content and face validity

This study emphasizes that the protocol for the cross-cultural translation of the self-reported questionnaire used in this study was Beaton's guidelines.[25] The last two steps of the guidelines were reviewed by an expert committee and pretested. The VFI-TH had a content validity tool for use in a clinical setting. Accordingly, this study followed a standardized cross-cultural translation protocol[25] that influenced the results.

Sensitivity

The sensitivity of the VFI-TH was 22.7 percent. The low sensitivity of the VFI-TH could have been affected by the following five main factors.

Originally, VFI found that the index could effectively detect vocal fatigue in individuals with a broad range of pathologies concerning the voice, i.e. muscle tension dysphonia, TVC scar, and spasmodic dysphonia. Vocal fatigue was primarily found in hyperfunction causes, i.e. muscle tension dysphonia (MTD) and spasmodic dysphonia. Other studies also found that individuals with these voice disorders often had vocal fatigue.[22,30-32] Meanwhile, our study mostly included neurological voice problems and TVC paralysis (Table 2). The participants in the voice disorders group had lesions, and we could not recruit patients with MTD or spasmodic dysphonia because of time limitations. Hence, those who did not have pathologies of hyperfunctional voice disorders experienced more vocal fatigue, which is different from the original VFI.[14] This study targeted voice disorders, which might have caused the low sensitivity.

Secondly, individuals tend to compensate for their voice problems to normal when voice problems occur for a more extended period, even though they may still be having voice problems, which might affect vocal fatigue detection. The VFI-TH in this study found that the sensitivity differed from the original[33] and other studies.[22,30-32] The voice disorders group showed that all participants had chronic voice problems.[34] Table 2 shows that 82% of participants experienced voice problems for more than two weeks. Participants might have adapted this dysfunctional voice into daily life usage automatically. Furthermore, the VFI-TH is a self-reporting tool that gives each participant the ability to decide to do the questionnaire themselves. In addition, participants may not be able to recall everything accurately when problems occur for some time.[35] In this study, the ability of VFI-TH to detect vocal fatigue after being interpreted was lower.

The third reason was the severity of voice disorders. The voice disorders group had already received medical treatment and/or voice therapy, which meant that their pathologies were already relieved and their voice problems had improved compared to the time they participated in this study. They could have perceived that their voices were better or that they had no voice problems. In such cases, participants might barely detect their vocal fatigue, as reflected in the VFI-TH reports. This effect was agreeable with Niebudek-Bogusz et al. in 2008,[36] which found that receiving voice therapy subjectively improved vocal outcomes as reported.

The fourth reason was a limitation of study time and the COVID-19 pandemic. In this study, we began to recruit participants while COVID-19 was spreading. Hospitals limited the number of patients who could go to the hospital and allowed emergency cases only. Hence, voice disorder patients who had to follow up for voice therapy postponed their appointments for a few months. These two situations limited research time, which affected many voice disorders groups and might have resulted in the low sensitivity of the VFI-TH.

The last factor was the SLP's lack of subjective voice assessment in the inclusion criteria. One of the subjective voice assessment tools usually used in the clinic is GIRBAS[37] (i.e., G: grade, I: instability, R: roughness, B: breathiness, A: asthenia, and S: strain). Thus, the lack of SLP voice assessment led to an insufficient number of participants with voice disorders. Participants with minimal voice disorders were recruited with a history of vocal pathologies diagnosed by an ENT doctor instead of being recruited for current voice problems, which might have improved over time.

Even though the VFI-TH for this study had low sensitivity, the SLPs could use it as an additional tool with other voice assessments in the clinic. For more effectiveness, the tool was suggested for patients with hyperfunctional voice disorders such as muscle tension dysphonia and spasmodic dysphonia. Therefore, low sensitivity in this study was influenced by all five factors, as described above.

Specificity

VFI-TH had high specificity to vocal fatigue in the normal group. The original VFI describes that the vocal fatigue score must pass parts 1 and 3 together. In this study, typical voice participants who had voice problems were in the acute phase (<2wk) (Table 2), which was agreeable with other studies which concluded that voice problems could occur in most people in a lifetime.[38-40] In the meantime, participants who joined this study experienced minimal voice problems that did not affect daily life or work. Besides, it was found that participants with normal voices who passed part 1 totaled seven and part 3 totaled 30, but none passed both parts 1 and 3 (Table 6). As described, the specificity of this study was 100 because we could not find participants who passed both parts 1 and 3. However, the VFI-TH can distinguish vocal fatigue among those with normal voices at risk of voice problems.

Reliability

The results show that the VFI-TH parts 1, 2, and 3 total items were .93, .87, .94, and .94, respectively. Interpreting a reliable level was acceptable.[41,42] Moreover, the reliability of parts 1 (.93) and 3 (.94) were agreeable with the original VFI[14] and other versions such as German,[16] Malayalam,[18] Tamil,[17] Hong Kong-Chinese,[21] Persian[19] and Croatian.[22] In contrast, Cronbach's α coefficient in part 2 might impact participants' confusion while scoring each item in part 2 with Thai words that may be difficult to understand. Even if the reliability of part 2 (.87) was not in agreement with other versions of the VFI, the value was accepted. Acceptable

reliability might be attributable to the use of a standard reliability process.

Conclusion

The VFI-TH has 19 items divided into three parts. Part 1 is related to the tiredness of the voice and avoidance of voice use. Part 2 is related to physical discomfort, while part 3 is associated with improving symptoms due to rest. The cut-off score for each part is different. The cut-off scores are ≥24 for part 1, ≥7 for part 2, and ≤7 for part 3. Individuals with vocal fatigue should meet the criteria for both parts 1 and 3. In clinical use, an SLP should clearly explain to individuals about the negative and positive words used in each part as follows: VFI-TH parts 1 and 2 use negative words. The higher the score, the higher the degree of voice problems. In contrast, part 3 uses a positive word. The lower the score, the higher the degree of voice problems. If the explanation is not clear enough, individuals might be confused and the test results might be misinterpreted. The VFI-TH was a valid and reliable tool. Sensitivity was 22.7%, and specificity was 100%. The VFI-TH can also be used with other voice assessments.

Limitations

In this study, data collection was carried out during the pandemic period of COVID-19, which could have affected the number of participants in the voice disorders group due to the low number of hospital visits and low yield in the number of patients with vocal cord lesions, muscle tension dysphonia, and hyperfunctional voice disorders, which ultimately could have affected the sensitivity of the study. The onset of the disease varied in the time range. This variation may have been due to the decreased self-awareness of individuals when reporting their vocal problems. Further research should be conducted concerning these factors.

Conflicts of interest

The authors declare that no competing interests existed at the time of publication.

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Guillain–Barré Syndrome in a patient with systemic lupus erythematosus with underlying pituitary carcinoid: A rare presentation

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ABSTRACT

Background: Guillain-Barré syndrome (GBS) is a rare neuropsychiatric symptom of systemic lupus erythematosus (SLE). GBS in individuals with SLE has distinct features than those without SLE. There is much heterogeneity in the treatment and clinical outcome. Even though GI carcinoids have been related with autoimmune illnesses, extra-gastrointestinal carcinoid coexisting with SLE has been documented only once, and coexistent GBS and SLE with pituitary carcinoid have never been reported previously to the best of our knowledge. Greater knowledge of how inflammation causes cytological alterations that contribute to the formation of a carcinoid might help explore newer pathological mechanisms and therapies.

Objectives: We report a middle-aged female who presented with sudden onset of weakness in all four limbs, long-standing history of arthralgia, flushing, dizziness, and a malar rash.

Materials and methods: The initial evaluation led to the diagnosis of GBS and SLE, for which the patient was treated. Further workup of patient revealed the presence of a carcinoid tumor in the pituitary.

Results: Patient was successfully treated with plasmapheresis, steroids, and injection octreotide.

Conclusion: In patients with SLE, neuropsychiatric illness may have a plethora of presentation including GBS. Recognizing such rare presentations and evaluating the possibility of a carcinoid tumor in presence of symptoms like a long-standing history of intermittent palpitation, dizziness, profuse sweating, and flushing, should alert the physician of an underlying carcinoid tumor, which could prove detrimental if left untreated.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune illness that affects various organ systems in our body. The presence of the central nervous system (CNS) involvement in SLE was first reported by Hebra and Kaposi in 1875. Neuropsychiatric symptoms are present in around 56.3 percent of SLE individuals.[1] The most common symptoms are cognitive dysfunction, headache and seizures.[2] Association of SLE with GBS has occasionally been reported in the literature.[3] Gastrointestinal (GI) carcinoids have been associated with autoimmune diseases like SLE.[4] Extra gastrointestinal carcinoids with SLE have been reported only once.[5] Here we possibly report the first case of GBS as an initial presentation of SLE with an underlying pituitary carcinoid.

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Case report

A 48-year-old lady came to our hospital with a history of frequent, short-lasting episodes of palpitation, dizziness, profuse sweating and flushing for the last four years, arthralgia affecting small and medium-sized joints for the last six months, shortness of breath not associated with chest pain or cough, and aggravated with exertion for last four months, and five days history of ascending weakness in all four limbs. She noticed difficulty climbing stairs and getting up from a sitting posture, which rapidly progressed to the weakness of both upper limbs in the form of holding and lifting objects, combing hair, and doing other routine activities. There was no bladder and bowel involvement. There were no complaints of diarrhea, abdominal pain, history of any dog bite, or recent vaccinations. She had no other comorbidities, and there was no similar presentation in the past. There was no history of abortions or stillbirth.

Clinical examination

The patient was attentive, aware, and communicative during the examination. There was mild pallor and an erythematous, non-itching malar rash. Icterus, cyanosis, clubbing, lymphadenopathy, and pedal edema were absent. Her pulse rate was 96 beats per minute, regular, and her blood pressure at the time of examination was 140/90 mmHg in the supine posture, and her respiratory rate was 26 cycles per minute. Examination of the central nervous system (CNS) revealed normal higher mental functions and no involvement of any cranial nerves. On motor system examination, the bulk was normal with hypotonia, and power was decreased (3/5) in all four limbs. All deep tendon reflexes (DTR) and superficial abdominal reflexes were absent, and plantar reflex was absent bilaterally. There were no signs of sensory, cerebellar, or meningeal involvement. The cardiovascular, respiratory, and per-abdomen examinations were normal.

Laboratory investigations

A complete blood count revealed hemoglobin (Hb) of 7.5 gm/dL, total leukocyte counts (TLC) of 3800 cells/µL, total red blood cell counts (TRBC) of $3.93x10^6$ cells/µL, and a peripheral smear showed microcytic hypochromic anemia. Urine routine and microscopy examination showed 3+ proteinuria and 1+ hematuria. Her fasting and postprandial blood sugar levels were 98 mg/dL and 120 mg/dL, respectively. Serum total bilirubin was 0.5 mg/dL, AST and ALT levels were 33 and 28 IU/L, respectively, serum sodium was 138 mEq/L, serum potassium was 3.5 mEq/L, ESR was 110, blood urea level was 28 mg/dL, serum creatinine was 1.2 mg/dL and eGFR 58 mL/min/m^2.

In view of ascending weakness of all 4 limbs with areflexia without bowel or bladder involvement, an urgent cerebrospinal fluid (CSF) analysis was done, which revealed albumin-cytological dissociation with a cell count of 5 cells/mm^3 and elevated CSF protein. A nerve conduction study (NCS) was also ordered, which revealed decreased distal motor amplitude and absent F waves, suggesting acute motor axonal neuropathy (AMAN) variety of GBS.

Considering clinical features such as arthralgia affecting small and medium sized joints, malar rash, and lab investigations suggestive of bicytopenia, proteinuria, microscopic hematuria suggestive of possible SLE, further workup was advised which revealed positive Antinuclear (ANA) and anti-ds DNA antibodies in high titers ≥1:100, nucleolar pattern, whereas C3 and C4 complement levels were decreased (0.3 gm/L, and 0.05 gm/L respectively) leading to a diagnosis of definite SLE according to 2019 European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) classification criteria. Antibodies to HIV, hepatitis B, and C were negative.

In view of unexplained intermittent dizziness, palpitation, profuse sweating, and flushing, the remote possibility of a neuroendocrine tumor (NET) was suspected, and an endocrine consultation was sought. 24-hr urinary 5-hydroxy indole acetic acid was sent, which was 20 µmol/day (normal range -10-40 µmol/day). An upper GI endoscopy was done, which showed only antral erosions. With a strong suspicion of NET, plasma serotonin and chromogranin A was advised, which turned out to be positive with values of 284 nmol/L (normal <30 nmol/L) and 700.1 ng/mL (normal <76.30 ng/mL) respectively, which was suggestive of a NET.

To localize the site of NET, CECT abdomen and thorax were done, which were normal. MRI brain and pituitary with contrast was done to rule out any CNS pathology, which showed a bulky left lobe of the anterior pituitary gland with a small nodular lesion measuring 9.4x8.7 mm, causing a slight deviation of infundibulum towards the right. The lesion showed an iso intense signal on T1W, iso to slight hyperintense signal on T2W with small cystic spaces within. The lesion showed gradual post-contrast enhancement in the dynamic phase, suggestive of pituitary microadenoma with cystic changes (Figure 1). Somatostatin receptor scintigraphy (SRS) with radio-labeled Ga-68-DOTANOC PET scan was not done because of unavailability. A final diagnosis of GBS (AMAN variety) with SLE & pituitary carcinoid was made.

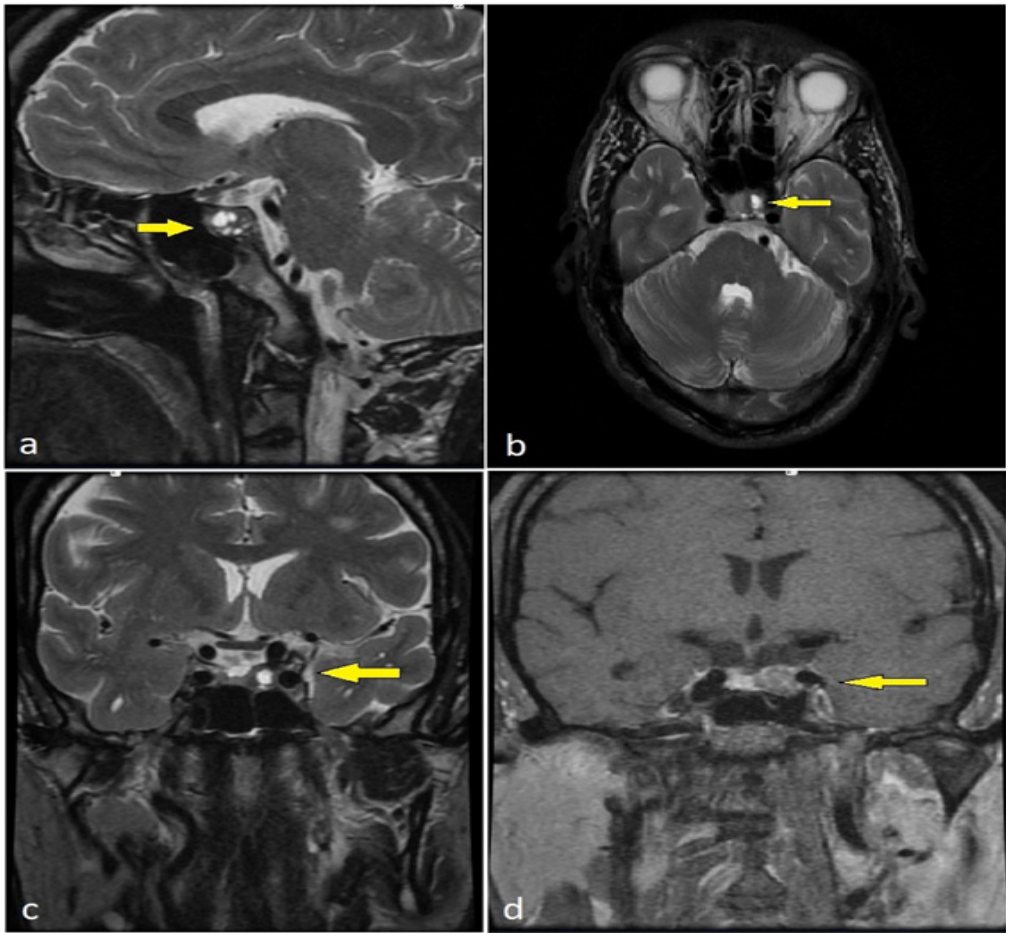

Figure 1. *MRI brain and pituitary with contrast showing a bulky left lobe of the anterior pituitary gland with a small nodular lesion measuring 9.4x8.7 mm, causing a slight deviation of infundibulum towards the right. a: sagittal T2, b: axial T2, c: coronal T2, d: coronal post-contrast enhancement in the dynamic phase suggestive of pituitary microadenoma with cystic changes.*

Treatment & follow up

For the initial five days, the patient received five cycles of plasmapheresis. The power of all four limbs started improving after the third cycle of plasmapheresis. By the end of the fifth cycle, her power had improved to grade 4/5. She was then given 1 gram of pulse methylprednisolone intravenously from day 6 to day 9. She was then started with oral prednisolone 40 mg/day, which was gradually reduced to 5 mg/day over the next 30 days.

At follow up after one month, there was a significant reduction in arthralgia. ESR was 22 mm, Hb improved to 9.9 gm/dL and TLC was 8600 cells/µL. Power and reflexes were also normal. For the treatment of pituitary carcinoid, after endocrinology consultation, injection Octreotide LAR 20 mg IM stat was given and planned for a repeat dose at the second month of follow up.

Discussion

GBS as a neurological complication is seen in 0.1% of patients of SLE.[1] GBS is often characterized by acute inflammatory demyelinating polyneuropathy, but in SLE, most GBS individuals have atypical features. Acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN) have been reported earlier in patients with SLE, where treatment with glucocorticoids and low-dose pulse cyclophosphamide has been beneficial.[6] Patients with SLE have been documented to have numerous neuropsychiatric manifestations like headache (most common), mood disorders, state of acute confusion, psychosis, cognitive dysfunction, cerebrovascular diseases, mono and polyneuropathy, seizures, autonomic disorder, myelopathy, cranial neuropathies, plexopathies, aseptic meningitis, demyelinating syndrome, movement disorders, and myasthenia gravis; being collectively referred as neuropsychiatric SLE (NPSLE).[7] A few cases of GBS as an initial manifestation of SLE has been reported in the literature.[3] Although the cause and mechanisms of GBS in lupus is unclear, it probably involves immunological pathways. As of now it's unclear whether GBS causes lupus flares or vice versa. Molecular mimicry leading to immune response because of cross-reactivity have been proposed as one of the mechanisms.[8] Second, a generalized and widespread immune response in SLE may result in the development of autoantibodies against gangliosides, which may cause demyelinating polyneuropathy resembling GBS. It is also hypothesized that complement activation and cell-mediated immunity play significant roles. Lupus vasculitis can lead to microangiopathy, and premature atherosclerosis which in turn accelerate ischemic demyelination triggering GBS.[9] Finally, host-specific variables including

genetics, ethnicity, and the environment may also be at play.

NPSLE is associated with high mortality rates despite aggressive immunosuppressive therapy making therapeutic plasma exchange (TPE) a safe and effective alternative.[10-11] Twenty-sex patients with SLE and CNS involvement who were given TPE alone or in conjunction with cyclophosphamide were analyzed by Neuwelt *et al*.[12] Following treatment, 74% of patients showed improvement, 13% were stable, and symptoms worsened in the rest 13%. The current American Society for Apheresis (ASFA) guideline considered TPE as a second-line therapy for SLE.[13]

Carcinoid syndrome is diagnosed by an excess of serotonin synthesis from a NET.[14] NETs are slow growing neoplasms with an incidence of 2.5 per 1,00,000 women and 2.0 per 1,00,000 men per year.[15] They originate most commonly from the gut, followed by the lungs, whereas 10% seem to have ectopic or an unknown origin.[16] Approximately 0.9% of patients with extra-pituitary NETs may develop pituitary metastases.[17] Urticaria, stomach pain, loose motions, edema of lips, bronchospasm, and variable blood pressure levels are common symptoms. Excessive urinary discharge of the 5-HIAA has generally been used to diagnose carcinoid with a sensitivity of 73% and specificity of 100%.[18-19] But in our case, 5-HIAA was normal which is often seen in an atypical carcinoid.[18] Consequently, a negative 5-HIAA result in a patient with clinical suspicion of carcinoid syndrome should be followed up with the measurement of plasma serotonin and chromogranin A levels, which are accepted as sensitive (90%) and specific (100%) markers of both functioning and non-functioning NET.[20-21] Due to the high expression of SSRs on NETs, receptor scintigraphy using somatostatin analogues as receptor ligands is a valuable diagnostic approach. Scintigraphy with 111-indium-marked octreotide or 68-Ga-DOTATOC provides a higher sensitivity (>90%) than CT/MRI for locating the primary lesion.[22]

Multiple studies have revealed a higher incidence of gastrointestinal carcinoids in autoimmune conditions like AIG.[23] The pathophysiology of the carcinoid-autoimmunity association can be explained by the fact that the patients with AIG have a chronic rise of serum gastrin due to gastric atrophy, which causes the development of gastric carcinoid.[23] However, this hypothesis explains the autoimmune mechanism for the gastric carcinoid only. None of the reported cases in the literature included development of extragastric carcinoids.

Carcinoid syndrome or NET are often misdiagnosed as irritable bowel syndrome (37%), intolerance to certain foods (18%) and psychiatric conditions (17%), or symptoms of menopause (5%), and the average delay in diagnosis is 5-7 years from the onset of the first recognizable symptom.[24-25]

This case is noteworthy for several reasons: the patient had intermittent flushing, sweating, dizziness, and dyspnea, which could be attributed to carcinoid disease. Pituitary carcinoid per se is uncommon, and its presence in a case of SLE-associated GBS is still rarer. A molecular understanding of how inflammation triggers cytological abnormalities that result in formation of carcinoids could lead to the development of novel therapeutic alternatives.

Conclusion

In patients with SLE, neuropsychiatric illness may have a subtle presentation ranging from confusion, lethargy, dementia, coma, and even GBS. Awareness of the likelihood of such rarer presentations, and a careful analysis of each documented clinical trait in individuals with a long-standing history of intermittent palpitation, dizziness, profuse sweating, and flushing in the presence or absence of hypertension, should alert the physician of a possible carcinoid tumor.

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Internet gaming disorder and its association with selected psychological problems among medical students

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ABSTRACT

Background: Playing games on the internet/smart devices has become an intrinsic part of our daily routine. Students and adolescents are identified as risk groups for Internet Gaming Disorder (IGD). Students of professional courses like medicine seem to be at a higher risk of the deleterious effects of IGD, but evidence for it is scarce.

Objectives: This study was conducted to find the prevalence of IGD, its risk factors, and its association with common psychological health problems among undergraduate medical students.

Materials and methods: In this cross-sectional study, the calculated sample were chosen through simple random sampling from each batch of undergraduate medical students. A semi-structured, pre-tested, self-assessment questionnaire was used to collect information. IGD was determined through the IGD-20 test scale and psychological problems using the DASS-21 scale.

Results: We included 220 students in the final analysis. The prevalence of IGD was 3.2% among the total population and 5.6% among those having risk. Students with IGD had significantly higher body mass indexes compared to those without IGD. A significant proportion of students with IGD had depression (85.7%) (p=0.007). Other psychological problems like anxiety and stress did not show a significant association with IGD in our study.

Conclusion: IGD is a newer disease entity, and since the at-risk population for IGD is growing day by day, this may pose a significant public health concern soon.

Introduction

Playing games on the internet/smart devices has become an intrinsic part of our daily routine. The gaming industry is booming as it provides services with many options/genres. Online or offline gaming is now highly accessible as one can play games on smartphones, tablets, laptops, desktop computers, and gaming consoles. It can be played alone, or with friends, the requirement of an internet connection is optional, and one can watch the other player playing in real time. Even the gaming platform is updated every few months with a high processing power chipset and an internet plan with fast internet surfing speed.[1]

In the last two decades, internet gaming has become the preferred leisure activity among kids and adults. Computer or smartphone-based games are pushing the world into a virtual reality as the gaming industry is rising exponentially

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to such an extent that in 2016 there were 120 million online gamers, and the estimated market value was around 290 million USD in India. At this pace, by 2021, it was speculated that the Indian gaming industry will add 190 million gamers and will become a one-billion-dollar industry.[2]

Internet gaming has its pros and cons. Few researchers found its positive effects like cognitive benefits, social benefits, and the development of leadership qualities among the players.[3] Some researchers even tried using games in pain management as a therapeutic measure.[4] The problem arises when these games are played excessively and create a possibility of addiction. There is now a considerable amount of evidence which states that heavy gamers develop psychological symptoms, which negatively impact their functional and social life.[5] The American Psychiatric Association recently recognized Internet Gaming Disorder (IGD) as a potential disease condition and found a place in the appendix of the Diagnostic and Statistical Manual, fifth edition (DSM-5), to encourage future research. World Health Organisation-International Classification of Diseases 11 (WHO-ICD 11) defined IGD as a "pattern of gaming behaviour ("digital-gaming" or "video-gaming") characterized by impaired control over gaming, increasing priority given to gaming over other activities to the extent that gaming takes precedence over other interests and daily activities, and continuation or escalation of gaming despite the occurrence of negative consequences".[6]

The prevalence of IGD varies widely. It is as low as 0.6% in Spain, to as high as 19.9% among adolescents in England.[7,8] Most of the studies worldwide have found a low prevalence of below 6%, while only a few studies reported a high prevalence of more than 10%.[9] Although Asian countries showed a high prevalence, India-specific data is lacking.[1] Studies have shown internet gaming to have a male preponderance and has been associated with poor self-esteem, increasing age, the academic performance of students, and disrupted family life.

In comparison to other internet-related disorders, gaming appears to be more associated with addiction and behavioural changes like depression, anxiety, stress, insomnia, irritability, loss of cognitive function, loss of appetite, social exclusion, and low productivity.[10,11] Students and adolescents are identified as risk groups for IGD. Students of professional courses like medicine seem to be at a higher risk of the deleterious effects of IGD, but evidence for it is scarce.[12] Moreover, associated risk factors and outcomes of IGD are yet to be revealed. Even identifying the vulnerable population to IGD may also help in designing preventive strategies in the future. This study was conducted to find the prevalence of IGD, its risk factors, and its association with common health problems in undergraduate medical students.

Materials and methods

A cross-sectional study was conducted in the Institute of Medical Sciences and SUM hospital with currently admits 150 students each year under the Bachelor of Medicine and Bachelor of Surgery (MBBS) course. All the undergraduate students of the MBBS course in the institute were our study population. The study was carried out under the short-term studentship program at the Indian Council of Medical Research (ICMR), India, from April to October 2019. The study was approved by the institutional ethical committee (Ref. No./DMR/IMS-SH/SOA/180058) and adhered to the Declaration of Helsinki's tenets. The sample size was calculated using STATA software version 13.

To the best of our knowledge, there were no studies (during the inception of the current research) eliciting the prevalence of internet gaming disorder in India. Studies in European countries showed a prevalence of 5% in the adolescent age group.[9] With an expected prevalence of 5%, alpha of 5%, power of 80%, and an absolute margin of error of 3%, the sample size was 203. The sample size was increased by 15% to 232 to compensate for the non-response or missing information. There are four batches (namely 3rd, 5th, 7th, and 9th semester) of undergraduate students in the institute, and to avoid bias, we selected 58 students from each batch for equal representation. Students from each batch were selected randomly by a computer-generated sequence (Microsoft excel 2007 software) using university roll numbers.

A semi-structured questionnaire was used to collect information and was pre-tested on 20 students (10% of the calculated sample size) for necessary correction and modification. The questionnaire was then incorporated into a digital platform using the Google form application and circulated among the selected students through email. Students were contacted twice telephonically or personally with a 7-day interval to submit their responses and those students who did not submit their responses after two contacts were categorized as dropouts/non-responders. The study rationale was clearly explained at the beginning of the questionnaire, and the students' consent was taken digitally as a binary response (yes/no) to fill out the form. We did not collect any identifying information through questionnaires, and the information given was anonymized.

The questionnaire/form was divided into five sections. The first section was used to collect general information like gender, residence status, type of family, family income, and academic performance in the last professional examination. The second section was intended to collect information on the health and lifestyle factors of the study participants like self-reported anthropometric parameters (height and weight), use of eyeglasses for refractive error, physical activity, food habits, and current disease conditions. Anthropometric parameters were used to calculate body mass index (BMI) in kg/m^2. The third section was to collect information on gaming behaviour like current habits, type of device used, online/offline gaming, duration, and type of game/genre played. The fourth section was to collect information regarding IGD using the IGD-20 test, which is a validated tool among adolescent and adult populations, summarizing six domains: salience, mood modification, tolerance, withdrawal symptoms, conflict, and relapse.[13-15] It has 20 questions, and responses to each question were captured on a 5-point Likert scale from strongly disagree to strongly agree. Two questions are reverse-coded before adding up all responses to questions to get the final score. The suggested cut-off point for the IGD was 71.[16] The fifth section collected information regarding common psychological

problems like depression, anxiety, and stress using the DASS 21 (depression, Anxiety, Stress Scale 21) scale, which is a well-established validated and reliable scale.[17,18]

The data collected was exported as a Microsoft excel file and analysed using SPSS version 20. All the categorical variables were expressed in terms of numbers and percentages. The association between the categorical variable was determined using the chi-square test/Fischer exact test. All the quantitative variables were expressed in terms of mean and standard deviation. The difference in mean in the two groups was obtained by using the t-test/ Mann-Whitney test. P-value <0.05 was considered statistically significant.

Results

Of 233 students, three students did not consent, four students dropped out of the study, and six students had some missing information. So, we included 220 students in the final analysis (non-response rate=5.6%). We got a 100% (58 of 58) response from 5th Semester students, followed by 7th (96.5%), 3rd (94.8%) and 9th-semester (87.9%) students.

Table 1 General characteristics of the study population.

Characteristics	Frequency (%) or mean (SD)
Age (years) #	21.36 (1.42)
Gender	
Male	106 (48.2)
Female	114 (51.8)
Residence	
Hostel	151(68.6)
Home	45 (20.5)
Own arrangement	24 (10.9)
Family type	
Nuclear	173 (78.6)
Joint	47 (21.4)
Family income (per annum in million INR)	
<1	61 (27.7)
1-2	105 (47.7)
2-3	26 (11.8)
>3	28 (12.7)
Body mass index (kg/m^2) #	24.57 (4.39)
Academic performance (out of 100) #	63.70 (6.62)
Physical Activity	
Regularly	55 (25.0)
Irregularly	131 (59.5)
Not at all	34 (15.5)
Eating junk foods habit	
Mostly (>once/week)	82 (37.3)
Sometimes (once/week)	125 (56.8)
Not at all	13 (5.9)
Habits*	
Smoking	24 (10.9)
Drinking alcohol	22 (10.0)
Other substance addiction	5 (2.8)
No addiction	187 (85.0)
Refractive Error	
Present	137 (62.3)
Absent	83 (37.7)
Other health problems*	
Hypertension	2 (1.0)
Asthma	11 (5.0)
Others	25 (11.4)

** Multiple responses, # variables represented in mean (SD).*

The mean age of the participants was 21.36±1.42 years and a slightly higher proportion of females (51.8%). The majority resided in the hostel (68.6%) and belonged to a nuclear family (78.6%). More than half of the participants were involved in irregular physical activity (59.5%) and eating junk food once a week. A considerably higher proportion (85%) had no addiction to substances and the rest were either addicted to smoking or alcohol or other substances. Almost one-third of the participants had a refractive error (62.3%). Other characteristics were shown in Table 1. Depression, anxiety, and stress were found in 43.2%, 44.1% and 27.7% of the students, respectively. Details of which were given in Table 2.

More than half of the students (57.3%) indulged themselves in online/offline gaming. We collected information regarding possible gaming devices present with the students and found that 71.4% had smartphones, 18.6% had desktop or laptop computers, and only 3.2% had gaming consoles. The majority of students involved in gaming played for less than 2 hours online (69.1%) and offline (50.8%) games. Most of them play action/combat games and discuss their gaming performance with fellow students (67.5%). Table 3 details the gaming behaviour of the study population. The prevalence of IGD was 3.2% among the total population and 5.6% among those having risk (Table 4).

Table 2 Prevalence of depression, anxiety and stress among the study population (N=220).

Severity	Depression N (%)	Anxiety N (%)	Stress N (%)
Normal	125 (56.8)	123 (55.9)	159 (72.3)
Mild	20 (9.1)	16 (7.3)	27 (12.3)
Moderate	47 (21.4)	45 (20.5)	18 (8.2)
Severe	18 (8.2)	13 (5.9)	10 (4.5)
Extremely severe	10 (4.5)	23 (10.5)	6 (2.7)

Among students suffering from IGD, 85.7% were male compared to 46.9%, not suffering from IGD without any statistical difference (p=0.058). We did not find any statistically significant difference for batch, residence status, type of family, and family income of the students with IGD (Table 5). Students with IGD had significantly higher BMI (28.0±5.26 kg/m^2) compared to those without IGD (p=0.035). Although the academic performance was lower in students with IGD, the difference was not significant (p=0.145). Lifestyle factors like physical activity, eating junk food, and addiction did not show any significant difference. Refractive errors and health problems were comparable between the students with and without IGD. A significant proportion of students with IGD were having depression (85.7%) than normal students (p=0.007). Other psychological problems, like anxiety and stress, did not show a significant association with IGD (Table 5).

Table 3 Gaming behaviour of the study population.

Gaming behaviour	Frequency (%)
Prevalence of online/offline gaming	126 (57.3)
Having assets for gaming *#	
Smartphones	157 (71.4)
Computers or laptops	41 (18.6)
Gaming console	7 (3.2)
No device for gaming	58 (26.4)
Average hours of online gaming per day#	
<2	87 (69.1)
2-5	15 (11.9)
>5	2 (1.6)
Average hours of offline gaming per day#	
<2	64 (50.8)
2-5	11 (8.7)
>5	1 (0.8)
The genre of games played*#	
Action/combat/real-time strategic	76 (60.3)
Massive multiplayer online	46 (36.5)
Sports	39 (30.9)
Roleplaying	10 (7.9)
Educational	16 (12.7)
Recreational/others	39 (30.9)
Discuss gaming performance with friends#	
Yes	85 (67.5)
No	41 (32.5)

** Multiple responses, # percentage regarding participants involved in gaming (126).*

Table 4 Prevalence of Internet Gaming Disorder (IGD) among the study population.

Population under consideration	Number	Prevalence (%)
Total population (N+220)	7	3.2
Those playing online/offline games (N=126)	7	5.6

Table 5 Association of different risk factors with IGD (N =220).

Variables	IGD present	IGD absent	χ^2 / t-value	*p* value
Gender				
Male	6 (85.7)	100 (46.9)	4.709	0.058
Female	1 (14.3)	113 (54.1)		
Semester				
3rd	2 (28.6)	53 (24.9)	3.098	0.377
5th	2 (28.6)	56 (26.3)		
7th	0 (0)	56 (26.3)		
9th	3 (42.8)	48 (22.5)		
Residence				
Hostel	4 (57.1)	147 (69.0)	0.448	0.799
Home	2 (28.6)	43 (20.2)		
Own arrangement	1 (14.3)	23 (10.8)		
Type of family				
Nuclear	7 (100.0)	166 (77.9)	1.964	0.350
Joint	0 (0)	47 (22.1)		
Family income per annum (in Million INR)				
<1	3 (42.8)	58 (27.3)	1.590	0.662
1-2	3 (42.8)	102 (47.9)		
2-3	1 (14.3)	25 (11.7)		
>3	0 (0)	28 (13.1)		
Academic performance (*mean±SD*) *	60.14±2.12	63.82±6.69	- 1.45	0.145
BMI (*mean±SD*) *	28.0±5.26	24.45±4.33	2.12	**0.035**
Regular physical exercise				
Absent	6 (85.7)	159 (74.6)	0.443	0.683
Present	1 (14.3)	54 (25.4)		
Eating behaviour				
No Junk food	3 (42.8)	135 (63.4)	1.221	0.429
Junk food	4 (57.1)	78 (36.6)		
Addiction				
Addiction	4 (57.1)	30 (14.1)	9.617	0.012
No addiction	3 (42.8)	183 (85.9)		
Refractive error				
Present	3 (42.8)	134 (62.9)	1.160	0.430
Absent	4 (57.1)	79 (37.1)		
Other health problems				
Present	5 (71.4)	(83.6)	0.714	0.335
Absent	2 (28.6)	35 (16.4)		
Depression				
Present	6 (85.7)	69 (32.4)	8.57	**0.007**
Absent	1 (14.3)	144 (67.6)		
Anxiety				
Present	3 (42.8)	78 (36.6)	0.113	0.710
Absent	4 (57.1)	135 (63.4)		
Stress				
Present	2 (28.6)	32 (15.0)	0.952	0.296
Absent	5 (71.4)	181 (85.0)		

**Mann-Whitney U test was used to calculate the p-value, and for the rest of the variables, a chi-squared/Fisher exact test was used.*

Discussion

The current study was an attempt to determine the prevalence of IGD and its associated risk factors among medical students. It is one of the few studies on students of professional courses in India. Studies conducted in Australia found a prevalence ranging from 1.8% to 7%,[17,18] those in Germany found a prevalence ranging from 1.2% to 7.1%.[22,23] A recently conducted meta-analysis found the prevalence to be 5% with a 95% CI of 3 to 6% (9). Although all these studies support our study findings but used other scales to determine IGD rather than the IGD-20 test. Recently conducted studies by Singh *et al*. and Aggarwal *et al*. on Indian medical students found a prevalence of IGD at 3.6% and 9%, respectively.[24,25] Both of these studies used IGD-Short Form (IGDS9-SF) to determine IGD. The higher prevalence by Aggarwal *et al*. may be due to a higher proportion (79.2%) of the study population involved in gaming compared to 57.3% in our study. Given the same socio-economic background, assets for gaming, social group, and prevailing student culture, IGD should be comparable among males and females. Our study failed to find a significant gender difference for IGD supported by other studies.[24,26]

Internet gaming disorder has been recognized as a behavioural disorder, which is gradually progressive and is thought to deteriorate over its chronic course. Literature suggests that such behavioural disorders may give rise to a wide array of physical and mental health problems. Psychopathological problems, especially depression, were more pronounced among addicted gamers than normal individuals, as reported by Lehenbauer-Baum *et al*.[27] Li *et al*.,[28] in their study, reported addicted gamers were more depressed and showed an escapist attitude. They concluded that the escapism attitude is mediated by their depression. Pathological gaming was significantly associated with substance abuse, as suggested by our study. A study conducted by Van Rooij *et al*.[29] found that adolescent boys using substances like alcohol, tobacco, and others had two times higher chances of becoming pathological gamers than the controls. They also found the same pattern among adolescent girls. Another significant study finding was the association of IGD with body mass index, which may be due to the long-time idleness among pathological gamers with reduced physical activity and disordered eating behaviour.[30]

The current study's strength lies in its methodology of selecting students using a simple random sampling method, which eliminates the bias of non-probability sampling reported in other studies.[24,25] Moreover, the non-response rate was low, at 5.6%. The use of a self-administered well-established validated questionnaire to determine IGD and psychological problems is an acceptable research method. Cross-sectional studies fail to establish causality or temporality but can pave the path for future research with a robust design to generate evidence for a causal association. The limitation of the study lies in its generalizability as the study was conducted on an elite group of the student population at a single centre.

Conclusion

After inclusion into the DSM 5 and WHO-ICD 11 classification, the current study is an attempt to explore IGD. We found a low prevalence of IGD in the study population, which was strongly associated with substance abuse, overweight/obesity, and psychological problems like depression. IGD is a newer entity, and since the at-risk population for IGD, is growing day by day, this may pose a significant public health concern soon. Hence, constant watch over it and future research to identify its health outcomes are needed.

Conflicts of interest

None declared.

Ethical approval

Approved by the institutional ethics committee of IMS & SUM Hospital, Bhubaneswar, Odisha, India.

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Telepractice program in voice therapy for primary school teachers: A Pilot study

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ABSTRACT

Background: Teaching is an occupation where teachers consistently use their voices. However, excessive voice use causes voice disorders, especially in primary school teachers. Therefore, to prevent voice disorder problems in teachers during the COVID-19 pandemic, voice therapy using telepractice was adopted so that teachers would gain knowledge and know how to prevent voice disorders.

Objectives: The main aim of this study was to develop and implement a pilot study on a telepractice program in voice therapy for primary school teachers.

Materials and methods: Telepractice program for primary school teachers was designed from the literature review under the theory of voice therapy for those people with voice disorders. Five experts with more than five years' experience in voice therapy tested the content validity, and five teachers undertook the entire program. Descriptive statistics were used to analyze the data.

Results: The results of index of item-objective congruence (IOC) for content validity in Part 1 (program outline), Part 2 (program manual), Part 3 (telepractice videos), and Part 4 (telepractice program quizzes) were 0.8, 0.89, 0.88, and 0.87, respectively. The IOC of the entire telepractice program was found to be 0.86, which passed the criteria. The try-out phase resulted in teachers suggesting adjusting their participation time to after 6 pm. for more convenience. Other suggestions for using voice for online and onsite teaching during COVID-19 pandemic were also provided, e.g., voice level control while using a microphone, a headset, and a computer setting during online teaching.

Conclusion: The pilot study of the telepractice program in voice therapy for primary school teachers passed the content validity test and try-out criteria for primary school teachers. Thus, the program could be used in voice therapy for teachers with voice disorders to eliminate program's efficiency in the next phase.

Introduction

Voice disorders occur when voice quality, pitches, and loudness are different or unsuitable for each individual's age, sex, cultural background, or domicile. Voice disorders are caused by the dysfunction or pathogenesis of vocal organs due to congenital anomalies, diseases, accidents, emotional and mental problems, vocal abuse, or unknown causes.[1,2]

Teachers are usually found with voice disorders because they must continually utilize their voices for teaching. Consequently, verbal communication all day long without a break causes teachers to have vocal fatigue.[3,4] Moreover, loud noises in school environments cause teachers to speak louder, resulting in shouting, vocal strain during phonation, and incorrect breathing

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during phonation. These issues imply hyperfunctional voice disorders.[4-7] If these ways of phonation are used for a long time while teaching until they become familiar, vocal abuse and misuse will occur, possibly leading to vocal injuries.[8]

From the data on the prevalence of voice disorders in teachers, Caitriona and Ray[4] reported that 27% of primary school teachers were usually found with voice disorders. According to De Alvear *et al*.,[3] 59% of kindergarten and primary school teachers in Spain had voice disorders. Likewise, Seifpanahi *et al*. found that 54.6% of primary and high school teachers in Iran had voice disorders.[9] In Thailand, Sajjaluck also found that 14.94% of primary school teachers had voice disorders. Additionally, Chantree and Hengphraphrom reported that 62.6% of primary school teachers had voice disorders.[10]

Speech and language pathologists play a crucial role in solving voice disorders for teachers who require voice therapy. Voice therapy approaches consist of 1) direct therapy, mainly focusing on voice practice behavior and reducing incorrect phonation behavior, i.e., education of hygienic voice therapy, symptomatic voice therapy with symptomatic treatment, and physiologic voice therapy as a holistic practice, and 2) indirect therapy, mainly focusing on emotional and mental states of those with voice disorders to direct them to correct voice therapy approaches in the long term.[11]

This pilot study aimed to develop a telepractice program in voice therapy for primary school teachers and brought the program to try out to improve the program. In particular, due to the current COVID-19 pandemic, there was no telepractice program in voice therapy for primary school teachers in Thailand. Hence, the researcher intended to develop an active practice approach to prevent voice disorders using telepractice. The communication technology method from telepractice aimed to facilitate speech and language pathologists to provide remote services for those with voice disorders. As such, for telepractice, the researcher combined a hybrid approach by using technology for synchronous practice with an asynchronous method to access the data at different times.[12,13] The researcher also viewed that primary school teachers should have comprehension and correct their vocal behavior in the long term under a telepractice program that would reduce costs, travel time, and exposure to COVID-19 for the correct use of voice in primary school teachers. Thus, the telepractice program in voice therapy for primary school teachers was implemented to examine and analyze its efficiency.

Materials and methods

This study was divided into two phases: 1) To develop the program and determine content validity and 2) to conduct a pilot study of the program.

Study design

This research was experimental research using a one-group pretest-posttest design. The study aimed to develop a telepractice program in voice therapy for primary school teachers and pilot it to improve any drawbacks before searching for its efficiency later.

Voice telepractice program

Researchers reviewed the literature on voice therapy principles for primary school teachers. Then, the telepractice program was developed, which consisted of four parts: Part 1: Telepractice program outline, Part 2: Telepractice program manual as shown in the examples of lesson 1 in Figure 1, Part 3: Telepractice videos as shown in examples of lesson 1 in Figures 2, and Part 4: Telepractice program quizzes. The telepractice program was divided into two sections as follows:

Section 1: Telepractice program training for 1.5 hours, which comprised introduction, vocal hygiene education with data about basic anatomy and physiology of phonation, videos of 10 situations presenting the incorrect use of voice for teachers, and a question-and-answer period at the end of the session (Table 1).

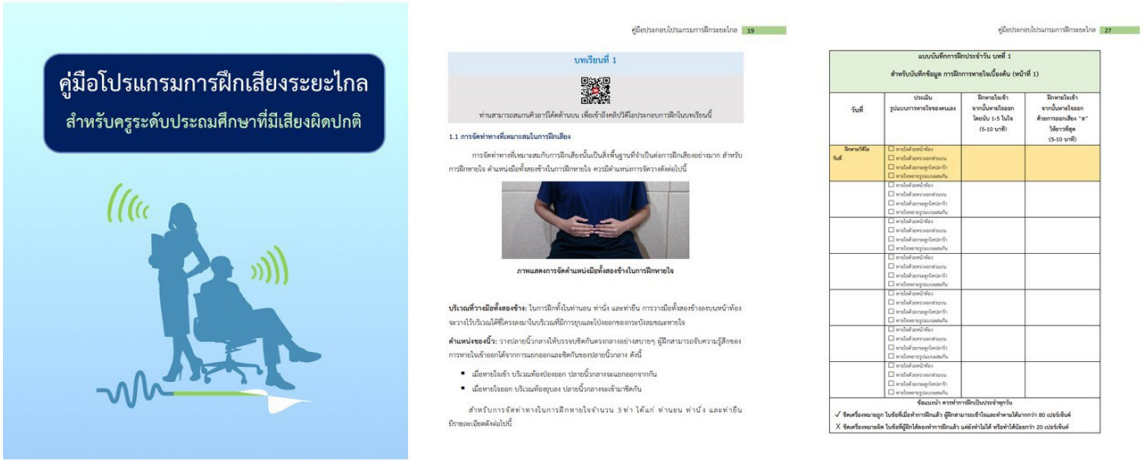

Figure 1 *Example of telepractice program manual in lesson 1.*

Figure 2 *Examples of telepractice videos in lesson 1.*

Table 1 Details about the telepractice program in Section 1.

Section 1: Timing and telepractice program training for 1.5 hours via Zoom cloud meetings		
Part 1: Introduction	- Official introduction of the project in terms of the detail procedures, implementation method, duration, and the end of the program.	15 minutes
Part 2: Vocal hygiene education	- Theoretical training. (The contents were about basic anatomy and physiology of phonation.)	15 minutes
	- Online workshop: - For vocal hygiene education and motivation of the comprehension to apply knowledge of vocal hygiene in real life. - Videos of 10 situations presenting the incorrect use of the voice were presented as the samples, e.g., how to avoid speaking in noisy environments and how to avoid speaking when exercising.	45 minutes
Part 3: Q & A session	- The researcher allowed the participants to ask questions about the telepractice program and all data obtained from the descriptions.	15 minutes

Section 2: Telepractice following the five lessons, one lesson per week, which had to be done twice a week (a total of 10 times) via YouTube for 30 minutes whenever the participants were convenient. The activities included group practice with speech and language pathologists for one hour via Zoom cloud meetings (Table 2). The participants would contact the researcher via LINE official. They were also required to complete Google Forms every time after the practice for self-assessment, answer the quizzes, and record the training to confirm their participation in each lesson. The researcher would check this part's data to monitor all the participants' results and to correct and provide more data for each participant in the following session.

Table 2 Details about the telepractice program training in Section 2.

Section 2: Practice Lessons 1-5 for 10 times twice a week	
Lesson 1 consisted of the following contents: - Posture for voice therapy - Relaxation technique - Basic breathing	Session 1: Practice Lesson 1 via YouTube for 30 minutes.
	Session 2: Group practice via Zoom cloud meetings for 60 minutes.
Lesson 2 consisted of the following contents. - Diaphragmatic breathing - Warm-up and warm down	Session 3: Practice Lesson 2 via YouTube for 30 minutes.
	Session 4: Group practice via Zoom cloud meetings for 60 minutes.
Lesson 3 consisted of the following contents: - Chewing method - Yawn-sigh method - Reduced glottal attack	Session 5: Practice Lesson 3 via YouTube for 30 minutes.
	Session 6: Group practice via Zoom cloud meetings for 60 minutes.

Table 2 Details about the telepractice program training in Section 2. (continued)

Section 2: Practice Lessons 1-5 for 10 times twice a week	
Lesson 4 consisted of the following contents. - Resonant voice therapy - Chant talk	Session 7: Practice Lesson 4 via YouTube for 30 minutes.
	Session 8: Group practice via Zoom cloud meetings for 60 minutes.
Lesson 5 consisted of the following contents: - Yoga voice - Vocal function exercises	Session 9: Practice Lesson 5 via YouTube for 30 minutes
	Session 10: Group practice via Zoom cloud meetings for 60 minutes.

Phase 1: Content validity

After four parts of the telepractice program had been developed, they were submitted for the content validity test by five experts (who had at least five years of specialization in voice therapy for those with voice disorders), i.e., two speech and language pathologists, two lecturers in voice disorders from the master's degree program, Faculty of Associated Medical Sciences, Chiang Mai University, and one otolaryngologist. The index of item-objective congruence (IOC) was considered. IOC >0.5 would pass the criteria.[14,15]

Phase 2: Try-out

After the experts and the revision determined content validity test was completed, the program was brought for a try-out for one week in January 2022 at Watsuandok school with five primary school teachers who used their voice in class for over four hours a day, five days a week.

In the try-out phase, within one week, the teachers had participated in vocal hygiene education once for 1.5 hours and asynchronous practice via Lesson 1 from an online video (the full version of the telepractice program included five lessons for 10 sessions) together with using of the manual. The participants were required to complete the data obtained by practice in the record form at the end of manual. Then, they completed Google Forms to record training data and to do the quizzes. Afterward, the participants assessed their comprehension with 6 parts of try-out and provided suggestions for the program in Google Forms. The 6 parts of the assessment are the Introduction of the program and vocal hygiene education, Zoom cloud meetings, telepractice program manual, telepractice video, quizzes and self-assessment, and overall convenience of use. Descriptive statistics were used to analyze the assessment data of 6 parts from participants with percentages. Next, the researcher took those suggestions for further improvement of this telepractice program.

Results

Phase 1: Content validity

According to the examined IOC, each item of the content validity test passed the criteria (Table 3).

Table 3 Content validity of the telepractice program.

Content validity			
Part	**Content**	**IOC**	**Conclusion**
1	Outline	0.80	Passed
2	Manual	0.89	Passed
3	Video	0.88	Passed
4	Quizzes	0.87	Passed
Total	All four parts	0.86	Passed

Phase 2: Try-out

Suggestions from all five teachers after the try-out and the scores of their comprehension in participation, zoom cloud meetings, manual, video, access to the assessment form and quizzes, and convenience of use based on their viewpoints are displayed in Table 4. All scores were over 80% in all items.

Table 4 Suggestions from the five users of the try-out phase.

Part	Comprehension Score (%)	Suggestion	Implementation
1. Introduction of the program and vocal hygiene education	83.89	- In reality, teachers could neither avoid any noises nor use their voice correctly in all situations from the videos of the 10 conditions about the incorrect use of the voice.	- Added an amplifier and a headset. - Added vocal hygiene education in online teaching.
2. Zoom cloud meetings	85	- No problem was found.	- -
3. Telepractice program manual	88	- No problem was found.	- -

Table 4 Suggestions from the five users of the try-out phase. (continued)

Part	Comprehension Score (%)	Suggestion	Implementation
4. Telepractice program manual	84	- Clear and attractive voice, but with noises sometimes, e.g., breathing practice in each posture.	- Revised as per the suggestion
5. Quizzes and self-assessment	88	- No problem was found.	- Added an amplifier and a headset. - Added vocal hygiene education in online teaching.
6. Overall convenience of use	92	- Convenient for use. - 4.30-6.00 pm. was the period that most teachers went home. Thus, it might not be convenient for their participation.	- Adjusted the participation duration to be more flexible after 9.00 pm. - Added concise information that should be practiced each week in the online assessment form at the end of the lessons. - Added an auto-alert notification in LINE Official for convenience and participants' comprehension of the summarized issues for practice each week.
Total	85.97		

Discussion

Phase 1: Content validity

From the content validity test by five experts, the score had to pass criteria score of 0.5, as shown in Table 3.[14,15] Thus, when considering the content validity of the entire program, it was found that the telepractice program for primary school teachers passed the criteria in terms of its content validity because the researcher reviewed the related literature and theories before setting the contents.

In Thailand, some voice programs emphasize that patients with voice disorders practice only breathing exercises through videos and manuals.[16] Lopez *et al*.[17] prepared the videos for a short training on vocal health in teachers; besides that, several researchers created a new manual for voice therapy in primary school teachers.[18-20] Many voice therapy programs have a vocal hygiene education session before participating in voice therapy.[17-21] It is essential content for teachers with voice disorders to understand and protect their vocal health. According to Liu *et al*.,[18] they have workshops with vocal hygiene education before attending direct voice therapy sessions with teachers.

So, in this research, the knowledge of voice telepractice program was designed from the theory of voice therapy and analysis from previous research studies about programs of voice therapy for primary school teachers, then rearrange the techniques from basic to advance with 5 lessons. Likewise, Lopez *et al*.[17] planned the program for 4 sessions starting with easy to difficult tasks such as vocal hygiene education, posture for voice therapy, breathing exercises with mindfulness and vocal training, and singing. Pizolato *et al*.[20] designed the techniques for the voice therapy program with 4 sessions as posture and cervical relaxation, respiration, phonation, and the last sessions with resonance and articulation. This research designed the practice of voice therapy for participants with 5 lessons. The practice of 5 lessons of the voice telepractice program, lesson 1: consisted of posture for voice therapy,[2,16,22] relaxation technique,[2] and basic breathing to improve the basics of breathing of primary school teachers.[22] Lesson 2: consisted of diaphragmatic breathing[22] and vocal warm-up and warm-down techniques[19,22-24] to prepare their voice before and after teaching in the classroom. Lesson 3: consisting of the chewing method,[2,24] yawn-sigh method,[2,25] and reduced glottal attack by the /h/ sound.[22,26] The main objective of this lesson is to reduce the incorrect habit of phonation in teachers. Lesson 4: consisted of resonant voice therapy[11,24] and chant talk[2,24] to increase the quality of phonation and find the suitable voice of frequency and loudness in participants. Lesson 5: consisted of yoga voice[2] and vocal function exercises,[22,24,25] in this lesson, the participants will practice advance techniques about pitch and overall method to maintenance voice quality in the long term.

For data suggested by the experts for revision in the telepractice program, Part 1: Telepractice program outline, the experts recommended changing the wording for better comprehension by the participants. As such, the data about hygienic voice therapy had to be rearranged, and redundancies or complicated words were deleted. For Part 2: Telepractice program manual, images had to be added to increase the clarity of the contents. Furthermore, the wording had to be changed for easier comprehension. Dangerous postures of muscle relaxation also had to be avoided, e.g., raising their head, which could be risky for those with cervical spine problems. Thus, the researcher deleted those challenging postures and added more cautionary warnings about unsuitable movements for some participants. Moreover, this program contained quite a lot of content. Thus, it was suggested to lessen the

number of words. For this reason, the researcher reduced those words, i.e., words, syllables, sentences, and articles.

For Part 3: Telepractice video, the brightness of video in some lessons had to be adjusted. The samples of incorrect or too similar voices in some parts of Lesson 4 were revised. For example, some monotones of the prototypes in the video were not different. The clarity of descriptions in video had to also be increased, that is, how many times they should be practiced for congruent comprehension in the sample viewers. In addition, for Lesson 4, a suggestion was made about having images to create an understanding of phonation.

Finally, for Part 4: Telepractice program quizzes, the experts suggested this part differently. For example, some suggested not using the names of people in the quizzes. Some advised not to ask, "Which one is correct or incorrect?" and use other quiz patterns instead. Some even suggested that the participants might not like quizzes at the end of the lessons. However, researcher's objective did not mainly focus on scoring but also on the exercise to examine the participants' comprehension and correct their miscomprehension of each class. Thus, the researcher reduced number of quizzes from five to three for each lesson. The deleted ones were those that seemed ambiguous or with unclear answers. Only the suitable ones remained. These were all revised and improved per the experts' suggestions for the try-out phase.

Phase 2: Try-out phase

According to the five teachers' comprehension assessment from the try-out phase, their total comprehension score was 85.97%, as shown in Table 4. The details of each part are as follows:

Part 1: Introduction of the program and vocal hygiene education received 83.89%. For the suggestions of this part, despite the concise and comprehensible objective, the teachers had to have time to participate in this long program. The teachers also said that activities suggested in the videos were suitable but could not be done in real life because primary school children were still hyperactive and could not control themselves like high school students. Teachers had to use their voices still to manage and teach these young children.

During the public relations of the try-out phase to find participants, the teachers mainly taught online. Then, they were required to teach onsite during the try-out week. This event made the researcher view both sides of the school environment. After talking with the participants directly during the post-program, it could be concluded that online content should be added to hygienic voice therapy to match the current COVID-19 pandemic. Proper voice control sentences while using the microphone should also be added in the videos of the 10 situations because the participants viewed that they still had to speak loudly despite utilizing a microphone. Likewise, Oliveira *et al*.[19] reported that teachers should use the amplifier as a microphone all the time in the classroom to reduce vocal problems. The participants also commented that vocal hygiene education and practice of all the lessons with speech and language pathologists in the evening had been set at 5 pm., but the teachers in the try-out phase informed that 4-6 pm. was period to go home and clear their work at school. Thus, it would not be convenient for any teachers to participate in the project during that time. For this reason, the researcher adjusted the practice time to after 6 pm. to facilitate the teachers who would join on weekdays.

Part 2: Zoom cloud meetings received a score of 85%. No suggestions were provided for this part. As for Part 3: Telepractice program manual scored 88%. Part 4: Telepractice video scored 84%. Lesson 1 suggested that it contained clear descriptions and clear voice but sometimes had noise. Thus, the researcher removed the noise as per suggestion. In accordance with Grillo[13] suggested that the media for telepractice as synchronous, synchronous, and hybrid should have good quality pictures, video, alphabet, and audio to benefit the participants. Finally, for Part 5: Quizzes and self-assessments in Google Forms scored 88%. In this part, the participants believed thequizzes suited the contents. Part 6: Overall convenience of use, Convenience to participate in the program achieved 92%. In this part, they viewed the program as useful for teachers with voice disorders (96%). Voice telepractice program for primary school teachers was a hybrid method from using synchronous zoom cloud meetings[27] and asynchronous as a private account of Line Application,[28,29] website of private YouTube channel[13] and Google Forms[30,31] to communicate with participants. All of the information in each week will send to them via Line Application with a video link of YouTube and Google Forms. Similarly, Grillo[13] reported that they used You tube to send the example of videos to patients in the telepractice program and used Google drive to keep the information from patients. It reduces times to go to the hospital and makes it convenient for patients to practice voice therapy at home during the COVID-19 pandemic.

Limitations

Because of COVID-19 pandemic, most of the teachers were very busy adapting their teaching methods, which affected the convenience of joining the program. However, in this small group of participants, the researcher still received helpful information to adjust the program to be more suitable for finding the program's effectiveness in the next phase.

Conclusion

It could be concluded that the telepractice program in voice therapy passed the content validity test by the five experts and was already improved as per the suggestions from the five users. Thus, the program could be used for the program's effectiveness in the next phase of research.

Ethical approval

This study was approved by the Research Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University (Approval ID: AMSEC-64EX-035).

Conflicts of interests

The authors declare that they have no conflict of interest.

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MRI evaluation of pediatric posterior fossa tumors and its correlation with histopathology: A prospective observational study

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ABSTRACT

Background: The commonest malignancy in the pediatric age group is leukemia, followed by brain tumors. Pediatric brain tumors are usually seen in children below 10 years. The incidence ranges from 1 to 3 per 100,000 cases. Primary intracranial tumors most commonly occur in the posterior fossa in children while infratentorial tumors are predominant in children over 4 years. Infratentorial tumors are more common overall, accounting for 45-60% of all cases. Physiologic characteristics of the pediatric posterior fossa tumors are well represented in advanced MRI techniques, which results in better pre-operative tumor evaluation, and often better results.

Objectives: Primary intracranial tumors most commonly occur in the posterior fossa in children. Treatment and prognosis rely heavily on correct diagnosis. The most important modality for early diagnosis is MRI of the brain. This study aims to evaluate the role of MRI in pediatric posterior fossa tumors.

Materials and methods: Thirty-three patients in the pediatric age group (<18 years) with a clinical suspicion of posterior fossa tumors, referred to the department of Radiology for undergoing MRI of the brain with contrast were included in the study. These patients underwent surgery followed by histopathological examination (HPE). Five parameters from conventional MRI were chosen and correlated with histopathology (gold standard). Statistical analysis was done subsequently.

Results: Diffusion-weighted imaging (DWI) is the most accurate parameter (94%), followed by T2 weighted imaging (T2WI), gradient, and post-contrast sequence (91% each). Diffusion-weighted imaging and post-contrast sequence had the highest specificity (almost 96%) while DWI and T2WI had the highest sensitivity (90% each). All 5 parameters are useful in 85% of cases. Overall diagnostic accuracy of MRI was almost 94% compared to histopathology.

Conclusion: DWI is the best parameter, followed by T2WI, gradient imaging, and post-contrast sequence. MRI is highly accurate in the evaluation of pediatric posterior fossa tumors. In centers where advanced MRI techniques cannot be performed, some parameters from conventional MRI can be selected that aid in diagnosis. Our study shows that judicious use of 5 parameters can increase sensitivity, specificity, and diagnostic accuracy of MRI for pediatric posterior fossa tumors.

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Introduction

The commonest malignancy in the pediatric age group is leukemia, followed by brain tumors.[1] Pediatric brain tumors are usually seen in children below 10 years.[2] The incidence ranges from 1 to 3 per 100,000 cases.[3-4] Primary intracranial tumors most commonly occur in the posterior fossa in children.[5] The location of the tumors is age dependent. In infants, supratentorial tumors are more common, while infratentorial tumors are predominant in children over 4 years. Infratentorial tumors are more common overall, accounting for 45-60% of all cases.[6,7] The histological types in pediatric brain tumors vary widely, contrary to in adults. The commonest posterior fossa (infratentorial) tumors are medulloblastoma, pilocytic astrocytoma (juvenile), brainstem glioma, and ependymoma.[1,3,7] Less common tumors include Atypical rhabdoid/teratoid tumor (ATRT), vestibular schwannoma, cerebellar gangliocytoma, dermoids, high-grade glioma, hemangioblastoma (HB), meningioma and metastatic lesions.[3]

Treatment and prognosis rely heavily on correct diagnosis. The clinical manifestations of posterior fossa tumors are gait disturbances, raised intracranial tension, and cranial nerve deficits, which depend on the location, size, and type of tumor.[5] Tumors of the brainstem which are aggressive, manifest as signs of pyramidal tract defect and eye movement disorders. The evaluation is related to the symptoms at presentation. If the child is younger and unable to speak regarding his/her symptoms, then the evaluation is mostly based on clinical examination, achievement of milestones, response to stimuli, assessment of the nervous system, presence of symptoms such as diplopia, hearing loss, etc. On the other hand, if the child is relatively elder and able to speak about his symptoms, then the diagnosis is relatively easier compared to the younger group. The diagnosis proceeds to the intracranial space-occupying lesion (ICSOL) much earlier due to the elicitation of history by the patient. Subsequently, a clinical examination is done, similar to the one in the younger age group. Once the provisional diagnosis of a posterior fossa tumor is arrived at, the next line of management is a contrast-enhanced MRI of the brain, which is the investigation of choice.

Conventional sequences on MRI are useful in the evaluation of location, extent, type of tumor as well as areas of brain involvement (white or grey matter or both).[3] Physiologic characteristics of the pediatric posterior fossa tumors are well represented in advanced MRI techniques, which results in better pre-operative tumor evaluation, and often better results. In centers where advanced MRI techniques cannot be performed due to cost/time factors or lack of technical expertise, often conventional MRI is the only modality of diagnosis. This study aims to evaluate the role of MRI in pediatric posterior fossa tumors and compare it with Histopathological examination (gold standard).

Materials and methods

This prospective, observational study was conducted in a tertiary care center, Department of Radiology, Institute of Medical Sciences (IMS), and SUM Hospital, Siksha 'O' Anusandhan (SOA) Deemed to be University, Bhubaneswar, Odisha, India. Informed consent was taken from all the patients undergoing the study.

Selection and description of participants

We applied the following formula to calculate the sample size:

$$n = (Z)^2 * p * (1-p) / (d)^2$$

where
- n = Sample Size
- Z = Normal curve value for 99% Confidence (2.576)
- p = Sensitivity of previous reference article (86.7%)
- d = Absolute error or precision (20%)

Based on the sensitivity (86.7%) of MRI in the diagnosis of posterior fossa tumors with histopathology (gold standard) observed in an earlier publication by Ahmad T *et al.* and with 99% confidence and 20% allowable error, the sample size was calculated.[8]

Applying the formula to our study, the minimum sample size was 20. However, we were able to collect 33 patients for our study.

Study population

Our study population included all the patients who were referred to the Department of Radiodiagnosis with a clinical suspicion of posterior fossa tumors, for undergoing a pre-operative MRI of the brain.

Inclusion criteria

In our study, we included patients of the pediatric age group (aged 18 years or below), with a clinical suspicion of posterior fossa tumors, who underwent contrast-enhanced MRI of the brain.

Exclusion criteria

All patients who had undergone prior surgery for the posterior fossa tumors (post-operative cases) or posterior fossa masses of non-neoplastic etiology, were not included in our study.

Technical information

Conduct of the study

Pediatric patients (<18 years), with a clinical suspicion of posterior fossa tumors, were referred to the Department of Radiodiagnosis, for undergoing MRI of the brain with contrast. After obtaining informed consent, MRI was done in a 1.5 Tesla MRI system (General Electric Medical Systems, Milwaukee, WI, USA). Gadolinium-based contrast was administered at a dose of 0.1 mmol/kg.

Thirty-three patients in the pediatric age group underwent an MRI of the brain with contrast during the study period. Interpretation of MRI is generally done by at least 2 radiologists. One of them is a resident/trainee who prepares the provisional report and the other one is a faculty/consultant in the department, who has either an MD or DNB degree in Radiodiagnosis and finalizes the report. Very often a lot of MRIs with findings are discussed with 2-3 more faculties/consultants who share their experience and discuss similar cases seen in the past as a reference point.

Once these patients underwent surgical excision of the mass followed by histopathological examination (HPE) of the specimen, MRI findings were correlated with histopathology (gold standard), and relevant statistical analysis was done.

MRI parameters were chosen to aid in diagnosis

Five parameters were chosen from the MR imaging that was most helpful in arriving at a diagnosis. These included:

1. **Location of tumor**: Whether the tumor is located in the midline or off midline. Medulloblastoma, ependymoma, and brainstem glioma are the tumors that have a midline location while atypical teratoid/rhabdoid tumor (AT/RT), juvenile pilocytic astrocytoma and hemangioblastoma have a more common off midline location. So, on MRI, if a tumor had a midline location, it was assigned to be one of medulloblastoma, ependymoma, or brainstem glioma, depending on other parameters. While an off-midline location is expected to be one of atypical teratoid/rhabdoid tumor (AT/RT), juvenile pilocytic astrocytoma, and hemangioblastoma
2. **T2 signal**: Tumors can appear hypo, iso, or hyperintense to grey matter on the T2 sequence. Medulloblastoma appears isointense on T2 while the rest of the tumors are hyperintense. So, if a tumor appeared isointense on T2, it was assigned Medulloblastoma while hyperintensity meant it could be any of the other tumors.
3. **Diffusion imaging**: Tumors were classified according to whether they show restriction or no restriction on diffusion imaging. Medulloblastoma is the only tumor that shows diffusion restriction while the rest of the tumors do not. So, if diffusion restriction was seen, the tumor was assigned as Medulloblastoma. If no diffusion restriction, it could represent one of the other 4 tumors. Although teratoid/rhabdoid tumor (AT/RT) can show diffusion restriction, we did not have any MRI diagnosis of AT/RT.
4. **Gradient sequence**: Tumors were classified according to whether they show blooming on gradient sequence. Ependymoma is the only tumor that shows gradient blooming. So, if blooming on gradient sequence was seen, the tumor was assigned as ependymoma. If there was no gradient blooming, it could represent one of the other 4 tumors. Although teratoid/rhabdoid tumor (AT/RT) can show gradient blooming, we did not have any MRI diagnosis of AT/RT.
5. **Post contrast sequence**: Tumors were classified according to whether they show enhancement (homogenous or heterogeneous) or no enhancement on post-contrast sequences. Low-grade brainstem gliomas do not show post-contrast enhancement. So, if there was no post-contrast enhancement, the tumor was assigned as brainstem glioma. If there was enhancement (homogenous or heterogeneous), it could represent any of the other 5 tumors.

A diagnosis of a particular posterior fossa tumor was given if it satisfied at least 3 out of the 5 parameters.

Statistics

Statistical analysis was done using IBM SPSS version 22. Validity parameters namely sensitivity, specificity, accuracy, and positive/negative predictive values were computed for various MRI sequences concerning histopathology. Numerical variables were expressed as mean and standard deviations and the categorical variables were expressed as frequency and percentages. Chi-square test was used to test statistical significance. The value of $p<0.05$ was considered statistically significant.

Results

As seen in Figure 1, almost 73% of the tumors were located in the midline while the rest 27% had an off-midline location. Amongst the midline tumors, the most common were brainstem glioma and medulloblastoma (41% each) followed by ependymoma (17%). Amongst the off-midline tumors, pilocytic astrocytoma was most common (78%) followed by atypical teratoid/rhabdoid tumor and hemangioblastoma (11% each). The location of the tumor helped to provide a clue to the diagnosis in almost 94% of cases, while in 6% it was not helpful.

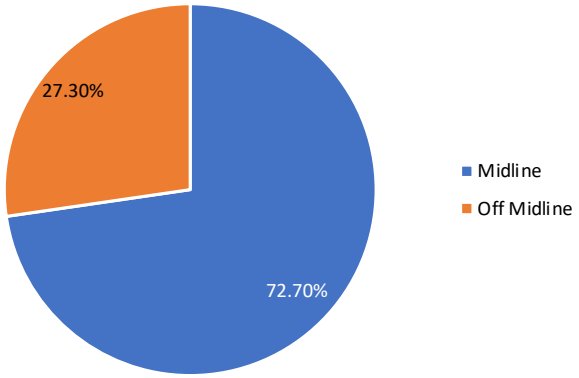

Figure 1. *Pie chart of location of posterior fossa tumors (n=33).*

One-third (33%) of the tumors were isointense on T2 weighted imaging while the rest two-thirds (66.67%) were hyperintense. As seen in Table 1, T2 weighted imaging had a sensitivity of 90% in predicting Medulloblastoma. Specificity was 91.30%, with a high negative predictive value of 95.45%. Overall diagnostic accuracy was 90.91%. Using the Chi-square test, a comparison of T2 weighted imaging and histopathology in diagnosing medulloblastoma was found to be statistically significant ($p<0.05$), as seen in Table 2.

In the gradient sequence, the majority of the tumors (almost 85%) did not show blooming, while only about 15% showed blooming. As seen in Table 3, the gradient sequence had a sensitivity of 75% in predicting the ependymoma. Specificity was 93.10%, with a high negative predictive

value was 96.43%, and the total diagnostic accuracy was 90.91%. Using the Chi-square test, a comparison of gradient sequence and histopathology in diagnosing ependymoma was found to be statistically significant (p<0.05), as seen in Table 4.

In our study, diffusion imaging showed restriction in about 30% of the patients. Rest 70% did not show diffusion restriction. As seen in Table 5, Diffusion imaging had a sensitivity of 90% in predicting medulloblastoma. Specificity was high at 95.65%, positive predictive value was 90%, negative predictive value was 95.65%, and total diagnostic accuracy was 93.94%. In our study, Diffusion imaging was helpful in diagnosis in almost 94% of patients. Diffusion-weighted imaging was the single most useful parameter in diagnosis. Using the Chi-square test, a comparison of diffusion-weighted imaging and histopathology in diagnosing medulloblastoma was found to be statistically significant (p<0.05), as seen in Table 6.

In post-contrast sequences, almost three-fourths of tumors (72.72%) showed enhancement and little over one-fourth of tumors (27.27%) did not. As seen in Table 7, post contrast sequence had a sensitivity of 80% in predicting brainstem Glioma. Specificity was high at 95.65%, and the total diagnostic accuracy was 90.91%. Using the Chi-square test, a comparison of post-contrast sequence and histopathology in diagnosing brainstem glioma was found to be statistically significant (p<0.05), as seen in Table 8.

As seen in Figure 2, In almost 85% of cases, all the parameters (sequences) were helpful in diagnosis. 4/5 of the parameters were helpful in 6% of cases. 3/5 and 2/5 parameters were useful in 3% of cases while none of the parameters were useful in about 3% of cases.

In our study, the overall accuracy of MRI in diagnosing pediatric posterior fossa tumors was almost 94% of patients. This is seen in Table 9.

Out of the total number of patients (33), the mean age in the study population was 6.6 years, ranging between 1 to 18 years. This is evident in Table 10.

Table 1 Validity parameters of T2 signal with histopathology in diagnosing medulloblastoma (n=33).

Parameter	Value (%)	95% CI	
		Lower	Upper
Sensitivity	90.00	55.50	99.75
Specificity	91.30	71.96	98.93
False positive rate	18.18	3.21	52.25
False negative rate	4.55	0.23	24.88
Positive predictive value	81.82	54.02	94.52
Negative predictive value	95.45	76.51	99.27
Diagnostic accuracy	90.91	75.67	98.08

Table 2 Comparison of T2 signal with histopathology in the diagnosis of medulloblastoma (n=33).

T2 Isointense	Medulloblastoma present (HPE diagnosis)		*p* value
	Yes	No	
Yes	9 (90%)	2 (8.7%)	<0.001
No	1 (10%)	21 (91.3%)	

Table 3 Validity parameters of gradient sequence with histopathology in diagnosing ependymoma (n=33).

Parameter	Value (%)	95% CI	
		Lower	Upper
Sensitivity	75.00	19.41	99.37
Specificity	93.10	77.23	99.15
False positive rate	40.00	7.25	82.95
False negative rate	3.57	0.18	20.23
Positive predictive value	60.00	25.99	86.50
Negative predictive value	96.43	83.14	99.33
Diagnostic accuracy	90.91	75.67	98.08

Table 4 Comparison of gradient sequence with histopathology in diagnosis of ependymoma (n=33).

Gradient blooming	Ependymoma present (HPE diagnosis)		*p* value
	Yes	No	
Yes	3 (75%)	2 (6.89%)	<0.001
No	1 (25%)	27 (93.10%)	

Table 5 Validity parameters of diffusion imaging in diagnosing medulloblastoma (n=33).

Parameter	Value (%)	95% CI	
		Lower	Upper
Sensitivity	90.00	55.50	99.75
Specificity	95.65	78.05	99.89
False positive rate	4.35	0.11	21.95
False negative rate	10.00	0.25	44.50
Positive predictive value	90.00	55.50	99.75
Negative predictive value	95.6	78.05	99.89
Diagnostic accuracy	93.94%	79.77	99.26

Table 6 Comparison of diffusion imaging with histopathology in diagnosis of medulloblastoma (n=33).

Diffusion Restriction on DWI	Medulloblastoma Present (HPE diagnosis)		*p* value
	Yes	No	
Yes	9 (90%)	1 (4.35%)	<0.001
No	1 (10%)	22 (95.65%)	

Table 7 Validity parameters of post contrast sequence in diagnosing brainstem glioma (n=33).

Parameter	Value (%)	95% CI	
		Lower	Upper
Sensitivity	80.00	44.39	97.48
Specificity	95.65	78.05	99.89
False positive rate	11.11	0.58	49.32
False negative rate	8.33	1.45	28.47
Positive predictive value	88.89	53.44	98.24
Negative predictive value	91.67	76.05	97.44
Diagnostic accuracy	90.91	75.67	98.08

Table 8 Comparison of post contrast sequence with histopathology in diagnosis of brainstem glioma (n=33).

No post contrast Enhancement	Brainstem Glioma Present (HPE diagnosis)		*p* value
	Yes	No	
Yes	8 (80%)	1 (4.34%)	<0.001
No	2 (20%)	22 (95.65%)	

Table 9 MRI diagnosis correlating to histopathological diagnosis (gold standard) among the patients (n=33).

MRI correlates to HPE	Frequency	Percentage (%)
Yes	31	93.94
No	2	6.06

Table 10 Distribution of age among the patients (n=33).

Parameter	Mean±SD	Median	Min	Max
Age	6.64±4.34	6.00	1.00	18.00

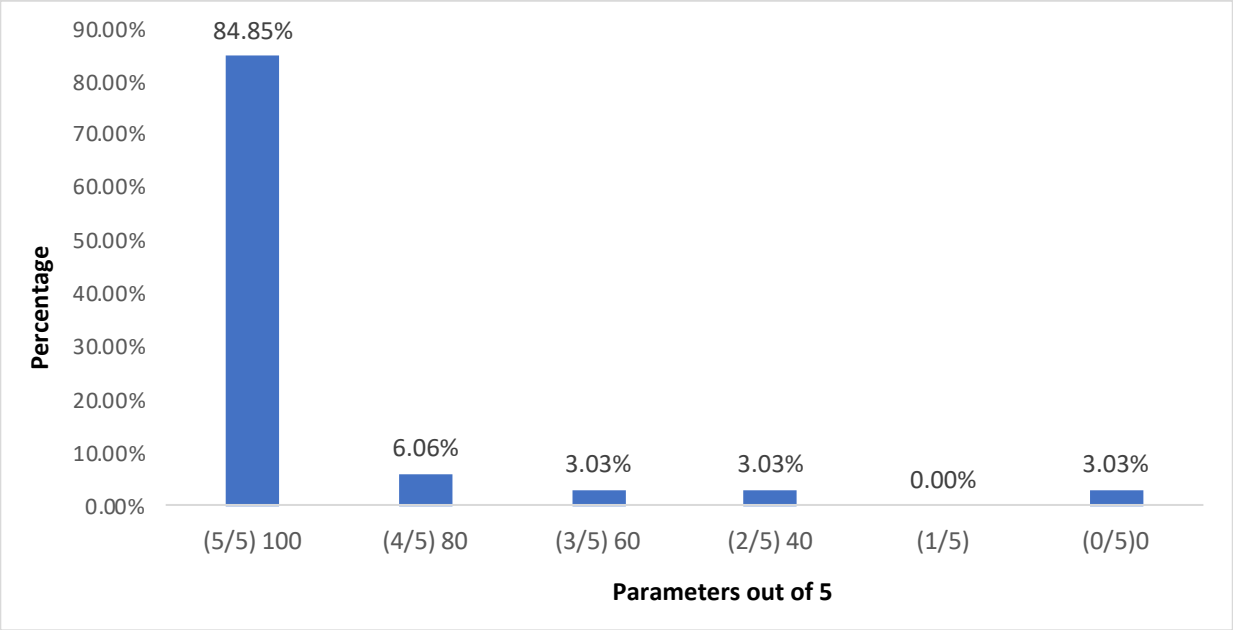

***Figure 2**. MRI parameters helpful in diagnosis (out of 5) (n=33).*

Discussion

In our study, the mean age of patients was 6.6 years. The range of age group was from 1 year to 18 years. According to Farwell *et al.*[2] the average age of onset is less than 10 years, which is seen in our study. There were slightly more males (51.5%) than females (48.5%) in our study, with a male-female ratio of 1.06:1. This is lesser than in the study by Farwell L *et al.*[2] where the ratio was 1.3:1, but slightly higher than the study by Yuh *et al*.[9] where it was 1:1.

Almost three-fourths (72.7%) of the tumors were located in the midline. Brainstem glioma and medulloblastoma were the most common midline tumors (41.67% each). All brainstem gliomas and medulloblastomas were located in the midline, which is slightly more than the studies by Levy RA *et al.*[10] and Poretti A *et al*. who observed that 75-90% of the medulloblastomas are located in the midline.[3] In our study, all cases of ependymomas were located in the midline, which is similar to Plaza J *et al.*[7] and Poretti A *et al*. who found that infratentorial ependymomas are located in the midline, on the floor of the fourth ventricle.[3] Amongst the off-midline tumors, 78% were pilocytic astrocytomas, while rare tumors such as atypical teratoid/rhabdoid tumors and hemangioblastoma constituted 11% each. This is similar to findings by Jaremko JL *et al.*[11] who found that a tumor located off midline is most likely to be pilocytic astrocytoma, and Meyers SP *et al.*[12] where most atypical teratoid/rhabdoid tumors were located off midline. The location of the tumors provided a clue to the diagnosis in 93.90% of the cases. Although Jaremko JL *et al.*[11] found that pilocytic astrocytoma was more likely to be off midline than medulloblastoma, they do not mention the full classification of tumors into midline or off midline and whether this parameter was used for diagnosis.

In T2 weighted imaging, almost one-third (30.30%) of the tumors were isointense, while the remaining 69.70% appeared hyperintense. Medulloblastomas are highly cellular and densely packed tumors, hence it is often T2 hypo to isointense compared to gray matter.[3,7] Hence tumors appearing isointense on T2 weighted images were assigned as medulloblastomas, while hyperintense T2 signal meant one of the other tumors. In our study, if a lesion was isointense on T2 weighted images, it was highly indicative of medulloblastoma, while 90% of the patients with medulloblastoma had an isointense signal on T2WI (sensitivity of 90%). The absence of isointensity on T2WI (hyperintense signal on T2) almost excluded medulloblastoma (very high negative predictive value of 95.45%). Moreover, 91.30% of patients who did not have isointensity on T2 weighted imaging did not have medulloblastoma (specificity of 91.3%). This is similar to the studies by O'Brien WT[1] Poretti A *et al.*,[3] Plaza J *et al.*,[7] Meyers SP *et al.*,[12] and Koeller & Rushing who report that most of the medulloblastoma's have iso to hypointense signal on T2WI.[13] The accuracy of T2 weighted imaging in diagnosing medulloblastoma was 90.91% compared to histopathology.

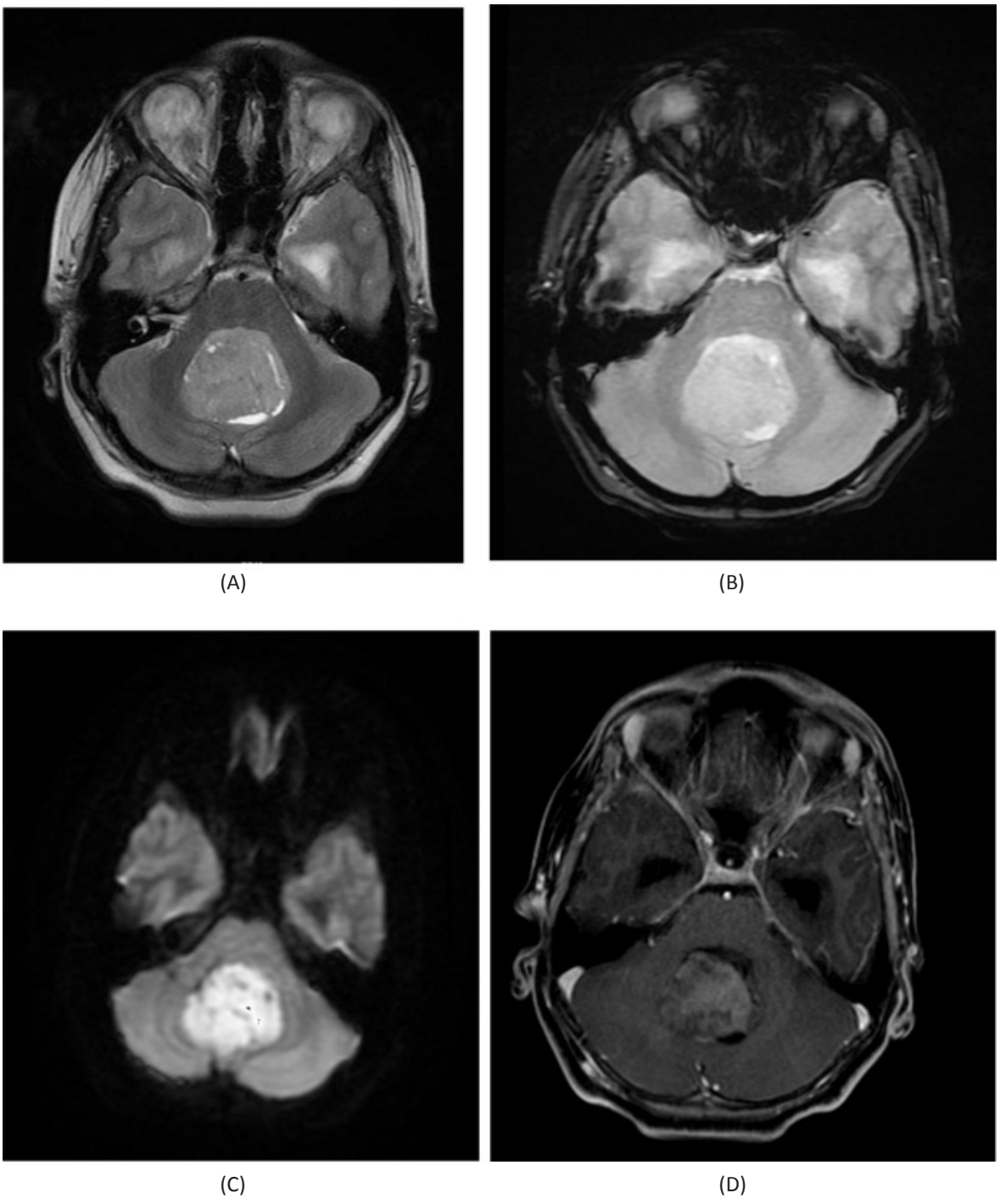

Image 1. Case of medulloblastoma. (A): axial T2 shows midline isointense mass, (B): axial SWAN sequence shows no blooming, (C): the mass appears bright on DWI (diffusion restriction), (D): post contrast sequence shows moderate enhancement.

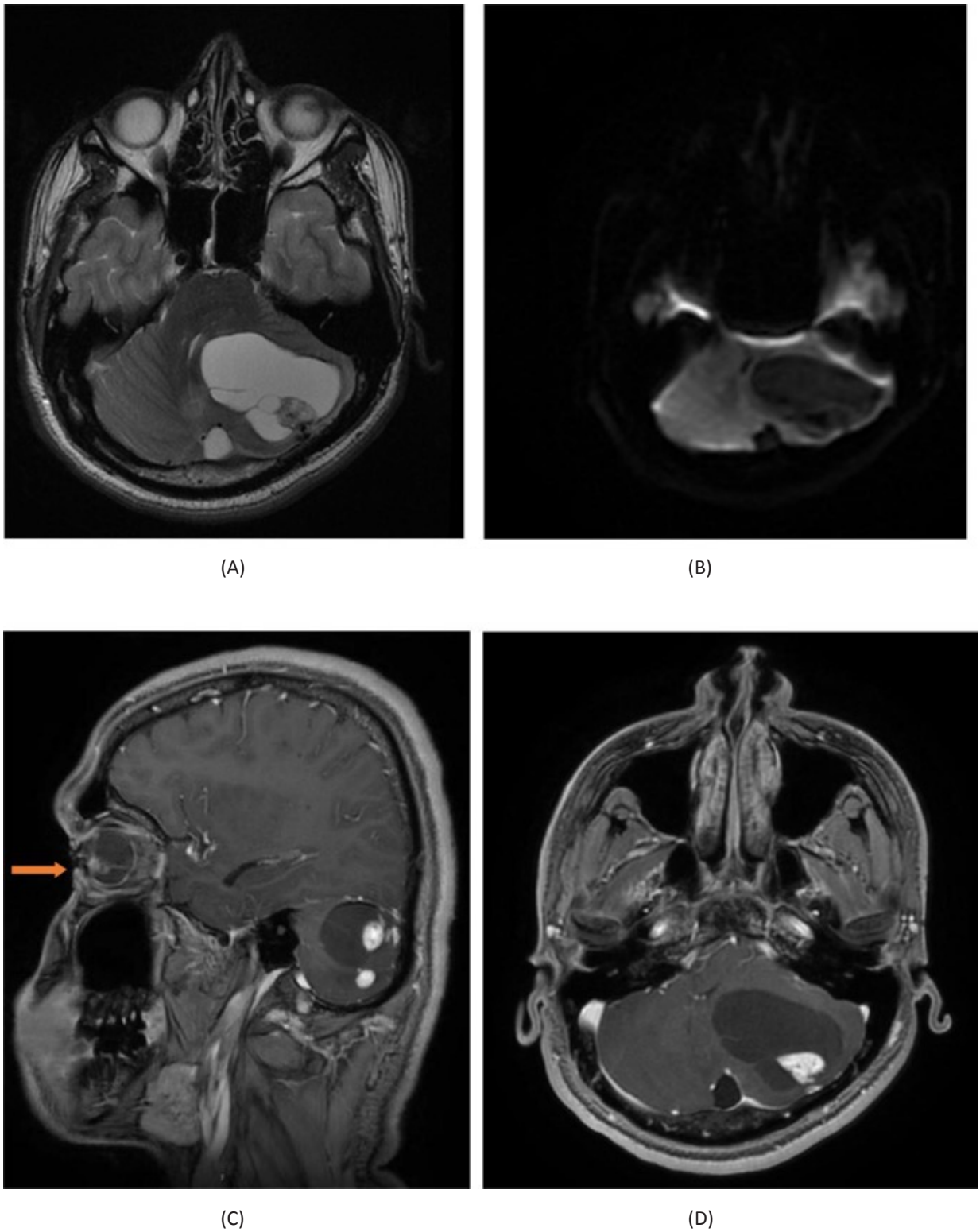

Image 2. Case of hemangioblastoma. (A): axial T2 shows left cerebellar (off midline) cystic mass with hyperintense nodules, (B): DWI shows no diffusion restriction, (C): left eye angioma (arrow), (D): post contrast sequence shows intense enhancement of the solid component. Patient was a known case of von Hippel-Lindau (VHL) syndrome..

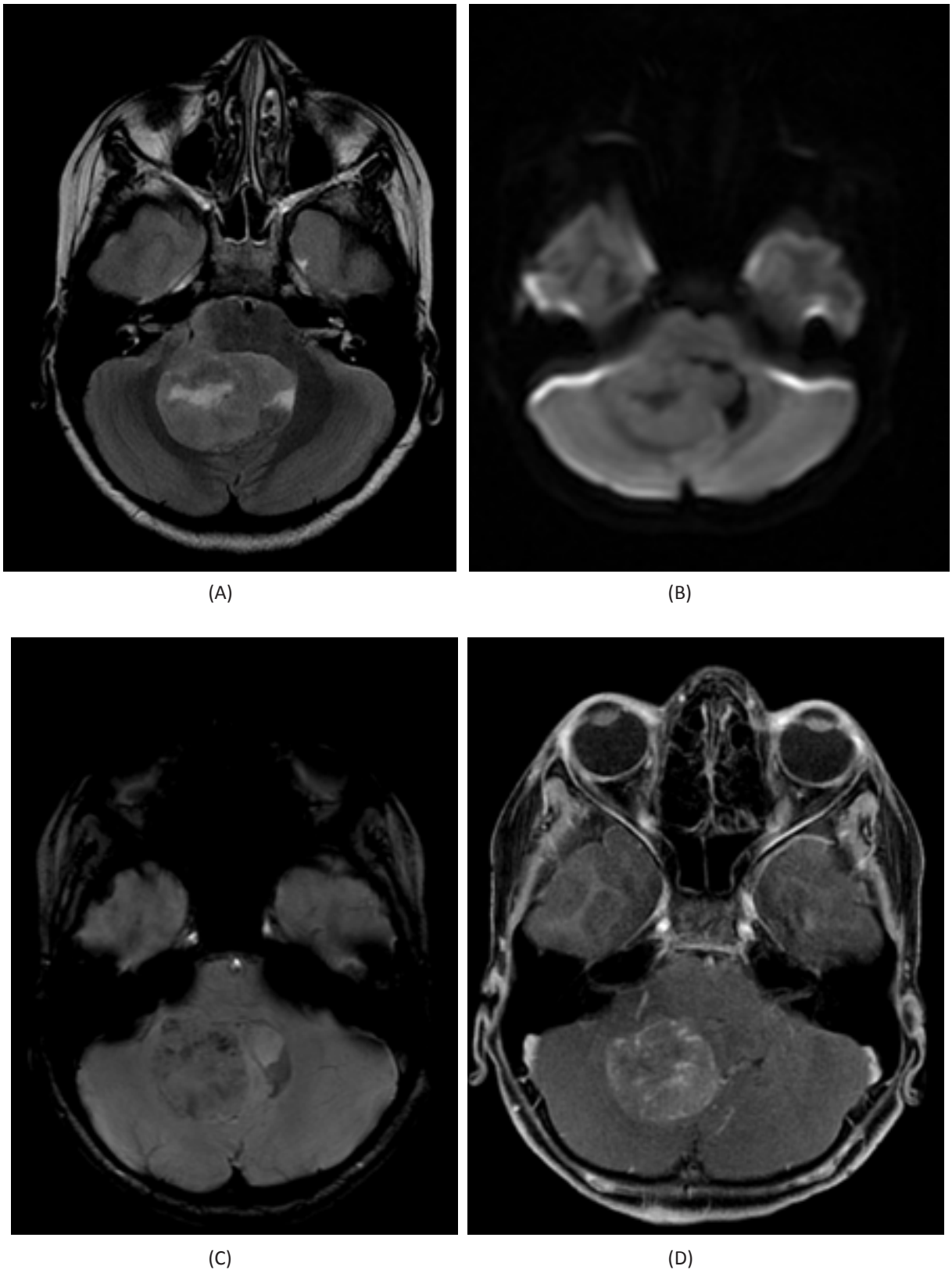

Image 3. Case of ependymoma. (A): axial T2 shows hyperintense midline mass, (B): DWI shows isointense mass (no diffusion restriction), (C): axial GRE sequence shows blooming, (D): post contrast sequence shows heterogenous enhancement.

Gradient imaging showed blooming in about 15.15% of tumors while the majority of the tumors (84.85%) showed no blooming. Plaza J *et al*.[3] found that calcification is seen in half (50%) of ependymomas. Hemorrhage & calcification bloom on gradient sequences. Hence tumors that showed blooming on gradient sequences were assigned as ependymomas, while the ones that showed no blooming, could represent one of the other tumors. In our study, 75% of ependymoma cases showed gradient blooming (sensitivity of 75%), specificity was high at 93.10%, while the absence of gradient blooming almost excluded ependymoma (very high negative predictive value of 96.43%). The sensitivity is higher than the study by O'Brien WT where calcifications are seen in about half (50%) of the cases, cysts in about 20%, and hemorrhage in 10% (total 60% blooming), and Poretti A *et al*. who found calcifications in about half (50%) and old hemorrhages, which appear as focal hypointensities on all sequences of MRI.[1,3] One of the differential diagnoses of medulloblastoma is ependymoma. In a study conducted by Koeller & Rushing it is seen that calcifications (which appear as blooming in gradient sequences) are typically seen in ependymomas, as opposed to medulloblastoma.[12] The diagnostic accuracy of gradient blooming in predicting ependymoma was 90.91%.

In our study, diffusion imaging showed that about 30% of tumors had restricted diffusion while the rest 70% showed no restriction. Koeller&Rushing found that medulloblastoma typically shows restricted diffusion on diffusion-weighted imaging (DWI).[12] Hence tumors that showed diffusion restriction were assigned as Medulloblastomas, while the ones that showed no restricted diffusion could represent one of the other tumors. In our study, diffusion imaging was very highly specific (95.65%) and sensitive (90%) for medulloblastoma. While the absence of diffusion restriction almost excluded medulloblastoma (very high negative predictive value of 95.65%). Our study had higher specificity than the study by Forbes *et al*. where the sensitivity and specificity of diffusion imaging in diagnosing medulloblastoma were 94% each, however, our sensitivity was slightly lower at 90%.[14] Our specificity was slightly lower than Camacho CA *et al*. who report that an apparent diffusion coefficient value of $<0.9x10^{-3}$ mm^2/sec is found to be 100% specific in differentiating medulloblastoma from astrocytoma and ependymoma.[15] Medulloblastoma typically shows restricted diffusion on DWI and lower values on apparent diffusion coefficient (ADC). This allows differentiation from ependymoma, pilocytic astrocytoma, and brainstem gliomas, as observed by Poretti A *et al*. and Plaza J *et al*.[3,7] Aquilina K found that high cellular density in medulloblastoma is seen as diffusion restriction on DWI. Jaremko JL *et al*. observed that in Ependymoma and Pilocytic Astrocytoma, the ADC values are higher than in medulloblastoma, and DWI-ADC is very useful to differentiate tumors of the posterior fossa in children.[11] Poretti *et al*. found that the ADC values of posterior fossa tumors in the pediatric age group can help differentiate the different types of tumors and predict their histological grades.[3] In our study, diffusion imaging had the highest diagnostic accuracy amongst all the parameters, at almost 94%, and hence was the single best parameter for diagnosis of posterior fossa tumors.

In post-contrast sequences, almost three-fourths of tumors (72.72%) showed enhancement, out of which 33.33% showed homogenous enhancement while 39.39% showed heterogeneous enhancement. Little over one-fourth of tumors (27.27%) showed no enhancement. Plaza J *et al*. report that most of the gliomas in the brainstem show no enhancement on MRI, and enhancement, is heterogeneous if it is seen in some cases.[7] Hence, any tumor that did not show post-contrast enhancement was assigned as glioma while if there was enhancement (homogenous or heterogeneous) could represent one of the other tumors. In our study, 95.65% of patients who did not have post-contrast enhancement did not have glioma, thus giving a very high specificity of 95.65%, while sensitivity was 80%. The presence of enhancement almost excluded brainstem glioma (high negative predictive value of 91.67%). This is similar to Poretti L *et al*.[3] who observed that enhancement in post-contrast sequences is variable, but most brainstem gliomas elicit minimal or no post-contrast enhancement. Camacho CA *et al*.[15] found that most of the gliomas of the brainstem do not show uniform enhancement. If there is some enhancement, the enhancing portion correlates to higher grades of the tumor. This is the reason for slightly lower sensitivity (80%) in our study as the 20% of tumors showing some enhancement (false negative) turned out to be medium or high grade. Aquilina K report that brainstem gliomas generally show no enhancement on post-contrast imaging.[5] The diagnostic accuracy of post-contrast enhancement MRI in predicting brain stem glioma was 90.91%.

All five MRI parameters namely, location of the tumors, iso-intensity on T2, gradient blooming, diffusion restriction, and post-contrast sequence taken together, were accurate in diagnosing almost 85% of the cases of posterior fossa tumors.

In our study, there were 31/33 cases were diagnosed accurately by MRI. Hence the overall diagnostic accuracy of MRI to histopathological examination (gold standard) was very high, at almost 94% (93.94% to be precise). This is slightly higher than the study by Forbes *et al*. who reported the predictive accuracy of MRI ranged from 78% to 93%.[14]

There were two cases whose MRI diagnosis did not correlate with histopathology. In the 1st case, the lesion was located in the pons (brainstem), was T2 hyperintense, no diffusion restriction or gradient blooming. No post-contrast enhancement was seen. MRI features were suggestive of low-grade glioma. As the tumor was growing rapidly in size, the biopsy was taken, which turned out to be grade IV medulloblastoma (PNET). None of the imaging features were suggestive of medulloblastoma. The patient later expired.

The 2nd case was predominantly a solid mass with cystic areas in the periphery and epicenter at the fourth ventricle. It was infiltrating the right cerebellar hemisphere, vermis, pons, and medulla with obstructive hydrocephalus.

On MRI sequences, it was hyperintense on T2, showed diffusion restriction and gradient blooming, and mild patchy post-contrast enhancement was seen. A provisional diagnosis of ependymoma was given. Histopathology was suggestive of atypical teratoid-rhabdoid tumor (AT/RT), which was later sent for IHC, which showed loss of INI-1, thus confirming the diagnosis. As AT/RT is a very rare posterior fossa tumor[3,7,12,16] it is very difficult to give it as a pre-operative diagnosis, based on just imaging findings. This patient too expired.

The differentiation of hemangioblastoma from pilocytic astrocytoma is challenging on conventional MRI. Hemangioblastoma and PA have overlapping imaging features. Subtle differences in the conventional MR imaging of hemangioblastomas are helpful in diagnosis such as extensive flow voids in and around the tumor, the mural nodule abutting the pial surface, and hemorrhage in about 20-25% of cases.[17] Further advanced MRI techniques such as increased perfusion and lower NAA/Cr values in MR spectroscopy aid the diagnosis. Clinically, association with von Hippel-Lindau (VHL) syndrome (44-72%) and higher age (hemangioblastoma is rare in children <18 years old) give a clue to the diagnosis. In our study, the patient was an 18-year-old child and a known case of von Hippel-Lindau (VHL) syndrome and had a large cystic lesion (T2 hyperintense) with peripherally enhancing nodules. There were few flow voids at the periphery of the lesion. No diffusion restriction or gradient blooming was seen while the nodules showed intense heterogeneous post-contrast enhancement. It is difficult to differentiate hemangioblastoma from pilocytic astrocytoma by just using the parameters chosen in our study. However, the overall morphology of the tumor, age, and clinical association of von Hippel-Lindau (VHL) syndrome aided the diagnosis. In such cases, advanced MRI techniques should be used, such as perfusion imaging (which will show increased perfusion) and MR spectroscopy (which will show lower NAA/Cr values) will help clinch the diagnosis.

There have been multiple studies on the role of MRI in pediatric posterior fossa tumors. But we did not find any study done previously, where specific sequences (parameters) chosen from the conventional MRI sequences were useful in predicting the diagnosis of tumors, especially where multiple individual parameters helped in diagnosis (like T2 helpful in the diagnosis of medulloblastoma, gradient for ependymoma, diffusion imaging for medulloblastoma and post-contrast sequence for brainstem gliomas). We selected sequences from the conventional MRI and used them to diagnose a particular tumor. In none of the previous studies, we found this kind of methodology, where single MRI sequences were useful in the diagnosis of a tumor. There were multiple such parameters chosen, each one helping in the diagnosis of a particular tumor. Hence, taken together, they help arrive at a diagnosis, which was highly predictive of the tumor, for histopathology (which is the gold standard for diagnosis).

With the results of our study, we searched for articles with a similar topic. From a lot of reference articles, we found that our results (usefulness of MRI in the diagnosis of pediatric posterior fossa tumors concerning histopathology, which is the gold standard) were comparable to previous studies, with most results better than others while the rest being at par. With such results comparable to standard reference published articles, we felt that our study is worth publishing too, as it provides something new, which is not seen in previous articles (multiple single parameters chosen from routine MRI sequences helpful in the diagnosis of multiple posterior fossa tumors). Moreover, there is no additional cost or time spent by the patient. The study population included cases that were sent to our department for MRI (who fulfilled the inclusion criteria). An accurate diagnosis can arrive fairly quickly as we used only the routine MRI sequences, that the patients were already about to undergo. This is vital in cases that require urgent surgical interventions. As proven in our study, since conventional MRI is highly accurate in diagnosing pediatric posterior fossa tumors, these patients can be taken up for emergency surgeries, right out of the MRI room (the report is usually prepared while the scan is going on, especially in emergency cases).

Conclusion

Diffusion-weighted imaging is the single best parameter helpful in the diagnosis of pediatric posterior fossa tumors (accuracy of almost 94%). It was followed by T2 weighted imaging, gradient imaging, and post-contrast sequence, all of which had accuracy of almost 91%. Together, all 5 parameters are useful in the diagnosis of 85% of cases. The overall accuracy of MRI in diagnosing pediatric posterior fossa tumors was very high at almost 94% for histopathological examination (gold standard).

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Impact of android app educational interventions on depression, anxiety and stress of recently detected type II diabetes patients

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ABSTRACT

Background: Persons with chronic disorders also suffer from undiagnosed mental health issues. Diabetes and stress are related to each other, people with diabetes mellitus have stress and stress in diabetes in turn affects their health. This study was conducted to assess the impact of android app educational interventions on depression, anxiety and stress among recently detected Type II diabetes patients.

Materials and methods: The study was a randomized controlled trial. Total, 66 subjects were recruited, 33 in both control and intervention group. The study group got interventions by using mobile application based software and control group got web-based intervention. All were counselled with lifestyle education by using printed educational materials. Depression, Anxiety and Stress Scale (DASS-21) was used in the study.

Results: Among the participants, 40.91% reported that they had at least one co-morbid condition. Only two participants had mental health issues. At baseline, 15.2% had depression, 43.9% had anxiety and 15.2% had stress, which were not different between control and intervention group. During follow up, the proportion of depression, anxiety and stress was decreased both in intervention and control group. In control group depression was decreased from 18.2% to 0%, anxiety was decreased from 45.5% to 4.5% and stress was also decreased from 18.2% to 4.5%. In intervention group, depression was decreased from 12.1% to 0%, anxiety was decreased from 42.4% to 0% and stress was also decreased from 12.1% to 0%.

Conclusion: Technology mediated educational interventions and involvement of clinicians may have a greater impact to improve the mental health in diabetes patients.

Introduction

Diabetes is a chronic incurable disorder of carbohydrate metabolism and Type II diabetes is the most common form of diabetes, accounting for 90 to 95% of all diagnosed cases of diabetes.[1] Type II diabetes is a progressive condition in which an individual's pancreas is not able to produce enough insulin, or body doesn't respond properly to insulin, called insulin resistance. It is a combination of ineffective insulin and lack of insulin. According to World Health Organization (WHO) fact sheet on diabetes, "an estimated 3.4 million deaths are caused due to high blood sugar".[2] Globally, the

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number of people with Type II diabetes is estimated to 387 million and is predicted to increase 592 million by 2035.[3] India is now severely affected by the global diabetes epidemic.[4] Diabetes is a disorder with multifactorial causes including both genetics and changes in lifestyle like diet, exercise and stress.[3,5]

Many individuals with chronic disorders also suffer from undiagnosed mental health issues.[6] Persistent stress may be the cause of serious illness. Stimulation in secretion of other hormones during stress raises glucose levels in blood. Diabetes and stress are much related to each other. Due to diabetes, patients take stress and such condition in diabetes also affects their health. Anxiety is the feeling of discomfort, worry, fearful thinking, apprehension of something with an undefined result; and stress is a state of psychological condition stemming from an unfavourable situation.[7] If the anxiety and stress are not properly managed, then depression develops in diabetic patients. According to the International Federation of Diabetes, it is important to implement psychological care for the management of diabetes.[8] Many studies have reported that depression enhances the risks of diabetes and anxiety and stress reported to have worsen the metabolic processes and escalate the complications in diabetes patients.[9-11] Proper assessment of mental health condition, counselling the patients and giving educational interventions are needed for diabetes management.[12] If self-care management of diabetes patients will be linked to technology, then they must be able to strengthen their physiological as well as psychological health. Some people face difficulties to use any app or website due to poor technical knowledge and low awareness regarding apps as a healthcare instrument, their own perceptions related to disease severity and other practical constraints like rural connectivity are the challenges for these type of studies. But now, some easy and simple android applications have been developed for boosting up patients' mental health by improving their awareness on diabetes.[13]

There are limited studies on mobile application for improvement of mental health among diabetic patients. So, a study was planned for the technical utilization of android applications by monitoring and guiding the diabetic patients for the management of diabetes and then reducing their stress. It was a hospital-based study, conducted to assess the effect of a mobile-based-application for the prevention of complications like stress, anxiety and depression among diabetes patients.

Materials and methods

Study design

In this experimental study, pre-designed, pre-tested and semi structured questionnaire was used which included DASS 21 scale to measure depression, anxiety and stress. Both qualitative and quantitative components were included in the questionnaire and the study was conducted from October 2016 to October 2018.

Study setting

This Randomized Controlled Trial was conducted in the Endocrinology and Community Medicine department of a tertiary care hospital.

Study population

Adult T2DM patients within 3 months of diagnosis, aged between 18 to 60 years, who visited endocrinology OPD during study period were included. Those who were assuming less techno-friendly and patients with cognitive impairment, any severe chronic diseases were not included in the study.

Sample size

The sample size was 54 patients for this two-treatment parallel-design study. With a dropout rate of 20% at the maximum during follow up over time, an additional number of 11 patients were added up and the total required sample size was 65 or roughly 33 for each arm.

Methods

After obtaining written consent, patients were randomized to control and intervention group. The sample size of 66 was divided into 11 blocks and 6 in each block. The 6 subjects within each block were assigned to website/ mobile group by random sequence generation 3 to control and 3 to intervention group. Sequentially numbered, sealed, opaque envelopes (SNOSE) were used to secure adequate allocation concealment.[14] Total 11 envelopes were prepared for 11 blocks and randomly generated sequence of control and intervention (eg. ABABBA) labelled papers were kept in that envelope. The investigators counselled all participants regarding lifestyle education by using printed educational materials. Intervention group participants were allowed to use android app and control group were told to use website named tunediabetes.com. The mobile based application included general personal data, diabetes related data, laboratory test data, online chat option and reminder for medication and exercise. The general personal data included socio-demographic profile, history of other chronic conditions, diet, sleep, exercise and anthropometry like BMI, waist circumference and diabetes related data included blood sugar, HbA1C etc.

There was also provision of all information related to complications of diabetes and its prevention. The control group was provided with an online platform in the website which included options for recording data similar to that of the mobile application except for the provisions like reminders.

The intervention group participants were contacted every 3 weeks for 3 months over telephone by principal investigator and were enquired about lifestyle change and counselled if required. Home visit was provided to the intervention group by the research team before first follow up and second visit was also done for missing cases. Baseline data collected and at every 3 months interval in one year (4 times), follow up conducted. Details of participant recruitment and follow up was mentioned in Figure 1.

Data collection tools and measurements

The study tool consisted of socio-demographic data, risk factors, co-morbidities, complications and family history of diabetes mellitus. For the assessment of depression, anxiety and stress, a validated DASS-21 questionnaire in local Odia Language was used. The DASS-21 questionnaire has 21 items,

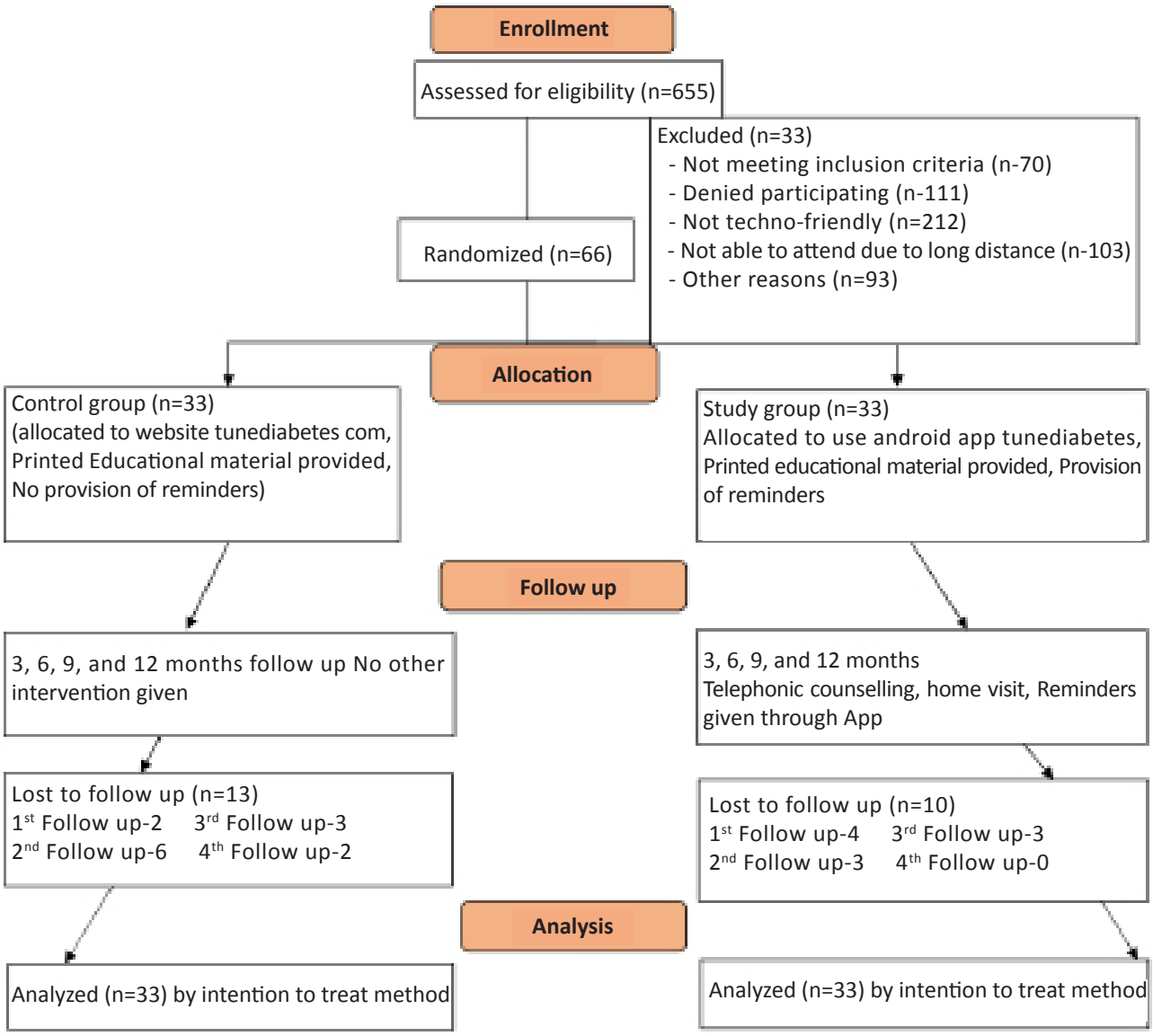

Figure 1. *Details of participant recruitment and follow up.*

assessing the symptoms of depression, anxiety and stress respectively. The participants rated their experience on every symptom on a 4-point severity scale ranging from '0' (does not apply to me), to '3' (applie s to me most of the time). Scores of each scale were summed up then and categorized as normal, mild, moderate, severe and extremely severe according to the DASS manual.[15]

Ethical approval

This randomized controlled trial was approved by the "Institutional ethics committee" as well as registered in "Clinical Trial Registry of India". The ethics committee code and the clinical trial registration number were DMR/IMS/-SH/SOA/16006, CTRI/2017/02/007911 respectively.

Data analysis

Data were analysed by SPSS v 20 licensed to our university. Descriptive analysis, repeated measures ANOVA test were applied to analyse continuous data and for categorical data proportions and Cochrane Q test was used.

Results

Total 66 subjects were recruited in the study, of which 33 were enrolled into control and 33 into intervention group.

Out of 66 study subjects, 65.2% were male and the mean age of the study subjects was 42.29±9.5. More than 95% were Hindus. Around 89.4% of the study subjects belonged to general caste; and 57.6% lived in joint family. Majority (89.4%) patients were married. Only 63.7% were educated up to graduation or master degree level and the mean per capita income was 11,545 Rupees (Table 1). There was no difference found between control and intervention groups in socio-demographic characteristics.

Table 1 Socio-demographic characteristics of participants.

Variables		Overall (n=66) n (%)	Control (n=33) n (%)	Intervention (n=33) n (%)	Significance
Age in years (Mean±SD)		42.29±9.5	42.88±9.5	41.70±9.6	0.617
Gender	Male	44 (66.66)	23 (69.7)	21 (63.6)	0.601
	Female	22 (33.33)	10 (30.3)	12 (36.4)	
Religion	Hindu	63 (95.5)	31 (93.9)	32 (97)	0.500
	Others	3 (4.5)	2 (6)	1 (3)	
Caste	General	59 (89.4)	29 (87.9)	30 (90.9)	0.509
	SC	3 (4.5)	1 (3)	2 (6.1)	
	Others	4 (6.1)	2 (6)	1 (3)	
Family Type	Joint	38 (57.6)	22 (66.7)	15 (45.5)	0.083
	Nuclear	28 (42.4)	11 (33.3)	18 (54.5)	
Marital status	Single	7 (10.6)	5 (15.20)	2 (6.1)	0.230
	Married	59 (89.4)	28 (84.8)	29 (87.9)	
Education level	Secondary and higher secondary	24 (36.4)	15 (45.5)	9 (27.3)	0.125
	Graduate and above	42 (63.6)	18 (54.5)	24 (72.7)	
Socio-economic status	Upper	34 (51.5)	14 (42.4)	20 (60.6)	0.294
	Middle	23 (34.8)	14 (42.4)	9 (27.3)	
	Lower	9 (13.6)	5 (15.2)	4 (12.1)	

Out of all subjects, 40.91% reported that, they had at least one co-morbid condition like hypertension, hypothyroidism, cardio-vascular disease, obesity, urological problems, osteoarthritis, neurological disorder without cognitive impairments, etc. Two participants were having depression and were under treatment. While interviewing about the family history of diseases, 60.61% reported that their family members were having one or more health problems. Majority family members (45.45%) of the participants had diabetes and 18.18% having cardio-vascular disorders.

Sleep was adequate among 74.2% participants and no difference was found between control and intervention groups. Tobacco addiction was found in 28.79% participants and 25.76% participants were alcohol addicted in baseline and no difference was observed between control and intervention group. Based on DASS-21, 15.2% had depression, 43.9% had anxiety and 15.2% had stress and these were not different in control and intervention groups (Table 2).

In the present study, 28.78% participants were found to use tobacco in any form, 6.06% were using both smoke and smokeless tobacco products. 25.8% were current alcoholics and 3.03% were heavy drinkers. Among the participants, 16.66% smoked tobacco products daily, 18.2% were using smokeless tobacco products daily. Alcohol was consumed by 34.84% participants in their lifetime on any occasion, 25.8% and 15.2% patients were consuming alcohol in past 12 months and 30 days respectively. Alcohol was quitted by six participants (9.1%) due to health related factors.

Table 2 Sleep, addiction, and mental health of participants at baseline.

Sleep per day	Total (N=66) n (%)	Control (N=33) n (%)	Intervention (N=33) n (%)	Significance
Adequate sleep	49 (74.2)	26 (78.8)	23 (69.7)	0.398
Less sleep	17 (25.8)	7 (21.2)	10 (30.3)	
Addiction				
Tobacco -Yes	19 (28.79)	10 (30.30)	9 (27.27)	0.786
No	47 (71.21)	23 (69.7)	24 (12.12)	
Alcohol - Yes	17 (25.76)	7 (21.2)	10 (30.3)	0.398
No	49 (74.24)	26 (78.8)	23 (69.7)	
Mental health				
Depression	10 (15.2)	6 (18.2)	4 (12.1)	0.492
Anxiety	29 (43.9)	15 (45.5)	14 (42.4)	0.804
Stress	10 (15.2)	6 (18.2)	4 (12.1)	0.492

In our study, dropout rate was high; control group (33→20), intervention group (33→23) which may be due to repeated follow ups, rigorous daily diary maintenance and their personal issues. This might be addressed by counselling and motivating the patients by the health care providers. It was found that, proportion of participants with adequate sleep increased in both the groups after intervention. Participants with adequate sleep were increased from 78.8% to 85% in control group and 69.7% to 78.3% in intervention group. Tobacco and alcohol use in last 3 months among participants was enquired during each follow up and the proportion of tobacco and alcohol use was decreasing in both the groups. In control group, proportion of participants addicted to tobacco was decreased from 30.3% to 10% and proportion of participants addicted to alcohol was decreased from 21.2% to 0%. In intervention group, proportion of participants addicted to tobacco was decreased from 27.27% to 0% and participants addicted to alcohol was decreased from 30.3% to 0%.

During follow up the proportion of depression, anxiety and stress was decreased both in intervention and control group. During last two follow ups, in the intervention group, no one had mental health issues, but in control group, one had anxiety and one had stress. In control group, proportion of participants with depression was decreased from 18.2% to 0%, anxiety from 45.5 to 4.5% and stress from 18.2 to 4.5. In intervention group, proportion of participants with depression was decreased from 12.1% to 0%, anxiety from 42.4 to 0% and stress from 12.1 to 0. (Table 3)

Table 3 Sleep, addiction and mental health of participants at follow up.

Sleep per day	Control n (%)					Intervention n (%)				
	Baseline	1st Follow up n=31	2nd Follow up n=25	3rd Follow up n=22	4th Follow up n=20	Baseline	1st Follow up n=29	2nd Follow up n=26	3rd Follow up n=23	4th Follow up n=23
Adequate sleep	26 (78.8)	26 (83.9)	25 (100)	22 (100)	17 (85)	23 (69.7)	26 (89.7)	23 (88.5)	20 (87.0)	18 (78.3)
Less sleep	7 (21.2)	5 (16.1)	0 (0)	0 (0)	3 (15)	10 (30.3)	3 (10.3)	3 (11.5)	3 (13)	5 (21.7)
Addiction										
Tobacco -Yes	10 (30.30)	4 (12.9)	2 (8)	2 (9.1)	2 (10)	9 (27.27)	3 10.35)	2 (7.7)	1 (4.3)	0 (0)
No	23 (69.7)	27 (87.1)	23 (92)	20 (90.9)	18 (90)	24 (12.12)	26 (89.65)	24 (92.3)	22 (95.7)	23
Alcohol - Yes	7 (21.2)	5 (16.12)	3 (12)	2 (9.1)	0 (0)	10 (30.3)	3 (10.35)	3 (11.5)	1 (4.3)	0 (0)
No	26 (78.8)	26 (83.87)	22 (88)	20 (90.9)	20 (100)	(69.7)	26 (89.65)	23 (88.5)	22 (95.7)	23 (100)
Mental health										
Depression	6 (18.2)	2 (6.3)	0	0	0	4 (12.1)	1 (3.6)	0	0	0
Anxiety	15 (45.5)	5 (15.6)	1 (3.0)	1 (4.5)	1(4.5)	14 (42.4)	8 (28.6)	1 (3.0)	0	0
Stress	6 (18.2)	2 (6.3)	2 (6.1)	1 (4.5)	1(4.5)	4 (12.1)	4 (14.3)	1 (3.0)	0	0

When the recruited patients were asked about any other health problems they faced in last three months, majority of them told that they had not suffered from any health problems (Table 4).

Table 4 Participants suffered from health problems in last 3 months.

Suffered from health problems in last 3 months	Control n (%)				Intervention n (%)			
	1st Follow up n=31	2nd Follow up n=25	3rd Follow up n=22	4th Follow up n=20	1st Follow up n=29	2nd Follow up n=26	3rd Follow up n=23	4th Follow up n=23
Yes	6 (19.4)	5 (20)	4 (18.2)	3 (15)	9 (31)	4 (15.4)	6 (26.1)	7 (30.4)
No	25 (80.6)	20 (80)	18 (81.8)	17 (85)	20 (69)	22 (84.6)	17 (73.9)	16 (69.6)

Discussion

The present study had a concept of giving intervention by using the mobile app technology for improving the mental health patients with type II diabetes. The participants were newly diagnosed (within 3 months) diabetes mellitus patients and the feeling of anxiety and stress related to the disease were common among them. If the anxiety and stress are not managed properly then it may worsen the mental health condition. In our study, educational interventions were given to the participants by mobile app and website

to enrich the mental health in study and control group respectively. Health care professionals, patients and families should be prepared with adequate information to reduce risk factors, make every day necessary adjustments in daily dietary habits, physical exercises, proper medications, and manage complications of diabetes for good physical and mental health.[16]

Many studies revealed that psychological health problems like anxiety, stress, and depression are very common in diabetic patients than the normal population.[17-22] Early recognition and treatment of depression, anxiety and stress in type II diabetes patients are very essential because of its relationship with hyperglycaemia, diabetic complications and poor quality of life.[23-26] In our study, 40.91% reported having at least one co-morbidity like hypertension, thyroid disorders, cardio-vascular disease, obesity, urological problems, osteoarthritis, neurological disorder, and only two participants were having mental health issues. In our study, co-morbidity in patients of recently diagnosed type II diabetes was similar or higher than other studies.[23-26] About 60% reported that their family members had one or more health problems. Majority (45.45%) family members of the participants had diabetes and 18.18% had cardio-vascular disorders. Yang Q et al, reported that, collecting family history of diabetes could provide significant improvements in detecting undiagnosed diabetes with proper validation.[27] In the present study based on score ranges from the DASS manual, 15.2% had depression, 43.9% had anxiety and 15.2% had stress and were not different in control and intervention groups at baseline. The proportion of depression, anxiety and stress was decreased both in intervention and control groups. In control group depression was decreased from 18.2% to 0%, anxiety was decreased from 45.5% to 4.5% and stress from 18.2% to 4.5%. In intervention group, depression was decreased from 12.1% to 0%, anxiety was decreased from 42.4% to 0% and stress from 12.1% to 0%. Similar findings were shown by the study done by Bahety et al, in which depression, anxiety and stress were 26.6%, 40% and 19.4% respectively.[28] Our findings were similar with other studies, that anxiety was common in type II diabetes supporting the association between psychiatric illness and type II diabetes.[29,30] Similarly, stress percentage for female was 21.74% while for males it was 6.98%. This result showed that depression, anxiety and stress is a common health problem in type II diabetes which corroborates with findings of a study by Bahety P et al.[28] In a critical review the author explained that females have a higher prevalence and risk of depression compares to males and there are many factors have been connected for this gender difference including socio-cultural and biological factors.[31]

In control group, proportion of participants addicted to tobacco was decreased from 30.3% to 10% and proportion of participants addicted to alcohol was decreased from 21.2% to 0%. In intervention group, proportion of participants addicted to tobacco was decreased from 27.27% to 0% and proportion of participants addicted to alcohol was decreased from 30.3% to 0%. The favourable results may be attributed to awareness regarding consequences of alcohol and tobacco by mobile application and web based platform. A study reported that in terms of alcohol consumption, to some extent current drinking was an independent risk factor for depression. A study showed that a bi-directional relationship between alcohol use and stress and alcohol use was used as means of coping with life's stresses.[32,33] Diabetes self-care management like checking blood glucose level, doing regular physical activity, taking general and specific diet have been improved among diabetes apps users. A study revealed that, use of diabetes apps may be a useful approach to enhance awareness on diabetes and its complications which may ultimately improve self-care practice.[34] In our study, app users got regular information regarding their diabetes medications, check-ups, diet, physical activity through the app by the health care professionals to reduce the disease severity and make them psychologically stable. Findings of a study concluded that, mobile applications related to diabetes mellitus had the potential to enhance diabetes self-care management to maintain a healthier lifestyle.[35]

Conclusion

Mobile app intervention decreased the proportion of depression, anxiety and stress in both control and intervention groups. In today's era of mobile and internet, education through mobile will be a great help for decreasing the mental health related problems. Clinicians may counsel and convince the patients to use the health related applications for their problems. Future mobile application based interventional research is needed for different health issues.

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Conflicts of interest

No conflicts of interest.

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Hepatic lesion detectability in abdomen computed tomography: Investigation in low kVp single energy and low keV virtual monochromatic images generated from dual energy computed tomography using task-based image quality assessment in phantom

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ABSTRACT

Background: Low tube potential single-energy (SE) and virtual monochromatic image (VMI) dual energy (DE) abdomen CT images both improve the hepatic lesion detection by increasing the liver lesion contrast on images.

Objectives: To study the performance of low kVp single energy and low keV virtual monochromatic images (VMI) generated from dual energy acquisition to detect the hepatic lesion on abdominal CT imaging in phantom.

Materials and methods: The anthropomorphic liver with nodule inserted phantom with extension rings simulating the small, medium, and large patient was scanned under the SECT acquisition by varying the kVp from 70-120 kVp and for DECT acquisitions, three kVp combinations (80/-,90/-, and 100/Sn150-kVp). The series of 40-,50-,60-, and 70-keV VMI were generated from DECT data set. All images were used to assess the task-based image quality; task transfer function (TTF), noise power spectrum (NPS), and detectability index (d') with the diagnostic task to detect 15 mm diameter hyperattenuating hepatic lesion.

Results: The result showed that the TTF was higher in low kVp SECT while the lesion contrast was higher at low keV VMI -DECT. The noise magnitude remained constant for all kVp values in SECT, but it was dramatically increased as decreased the energy level from 70- to 40-keV in VMI-DECT. The f_{av} of NPS shifted to higher frequency when increasing the kVp and when increasing the energy level of VMI. The obtained d' was highest in low kVp SECT at 70-or 80-kVp.

Conclusion: The low kVp SECT provided the highest d' than that in low keV VM image from DECT in all phantom sizes where the highest d' was found at 70 kVp-SECT for small and medium phantom and at 80 kVp for large phantom. For SECT, reduced the kVp to 70- or 80-kVp improved the detectability index. The kVp combination in DECT impacts to the d' of VMI; at small phantom, the highest d' for each keV VMI was found at 80/Sn150 kVp acquisition and at larger phantom size, higher kVp on tube "A" is more favored.

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Introduction

Primary liver cancer is the sixth most-commonly diagnosed cancer and the third leading cause of cancer related death worldwide in 2020.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer comprising of 75-85% of cases. In current clinical practice, CT is commonly used as an imaging modality for accurate detection and characterization of liver tumors.[2-4] Therefore, the lower noise images and multiphase acquisition are required to detect small hepatic lesions.

The low tube potential (low kVp) technique has been introduced to improve the conspicuity of liver lesion in appropriate patient size and reduce the radiation dose to patient in clinical abdomen CT.[5,6] However, this technique can be challenged in large patient because the X-ray attenuation is more and thus requires increasing of mAs to maintain the image quality. Unfortunately, the greater increase in mAs may not be achievable in some CT system due to inherent engineering design that limits in maximum X-ray output at lower kVp.

Recently, dual-energy computed tomography (DECT) is considered a promising new development in CT that had a potential to improve detection an d characterization of liver lesion.[7,8] The introduction of third generation dual source dual energy CT system provided several new improvement features; a new 150 kVp for high voltage tube equipped with thicker tin (Sn) filter enables an improvement of spectral separation, higher X-ray tube current to overcome the limitation of maximum mA at low-kVp or ultra-high pitch settings. Therefore, possible kV combinations in this generation are generally at 80/Sn150, 90/Sn150, and 100/Sn150.

Lesion detectability can be assessed using task-based image quality with the human observer or mathematical model observer method. The detectability index (d') which is a task-based detection performance metric based on mathematical model observer, has been introduced and implemented for the assessment of low-contrast detectability in modern CT systems.[9-11] This metric can be quantified using of non-pre-whitening observer model with eye filter (NPWE) that incorporated the resolution in term of task transfer function (TTF), noise texture, diagnostic task, and viewing conditions.

The purpose of this study is to investigate the lesion detectability for small hepatic lesion in abdominal CT images acquiring at low-kVp single energy and low keV VM image from dual energy acquisition. The impact of different kVp in SECT and different kV combination in DECT was also investigated for various sizes of phantom.

Materials and methods

A. Phantom study

An oval shape semi-anthropomorphic liver nodule phantom (QRM Moehrendorf, Germany) with size of 300x200x100 mm in x-, y-, and z- dimensions, was used t quantify task-based image quality and detectability inde of hepatic lesion. The two extension rings with mediu and large sizes with outside diameters on X- and Y-axes o 350x250 mm and 400x300 mm respectively, were adde to closely simulate the larger patient habitus (Figure 1a). This phantom is comprised of the abdomen body wit respect to the density typically 35 HU +/- 5 HU at 120 kV. The liver part has CT No. approximately 90 HU at 120 kVp, containing the hyperdense liver nodules with the CT No. approximately 180 HU at 120 kVp. This contributes the liver and nodule contrast at approximately 90 HU at 120 kVp scan. The phantom was placed at the isocenter for each CT acquisition.

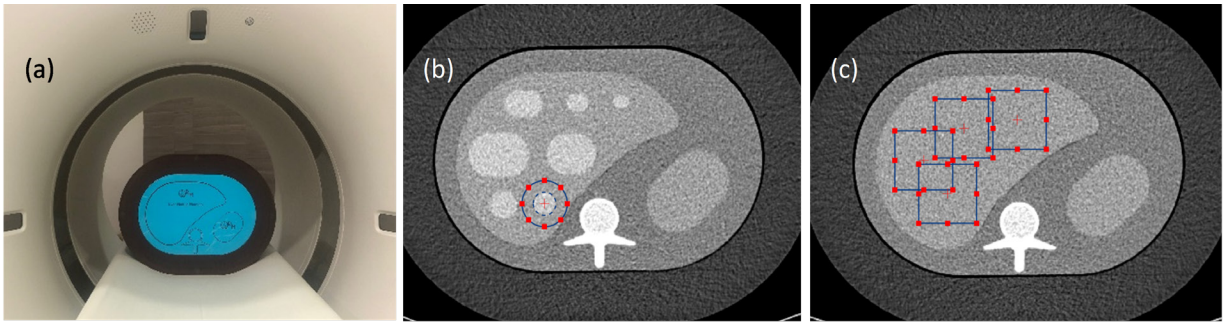

Figure 1 *Set up for phantom study. (a): liver nodule phantom equipped with the large extension ring (size L) placed at isocenter of CT scanner, (b): circular ROI placed on the 20 mm liver nodule insert to measure the TTF, (c): four-square ROIs were placed on the uniform area of liver phantom.*

B. CT Image acquisition and reconstruction parameters

The phantom was scanned by the third generation dual-source CT scanner (Somatom® Force, Siemens Healthineers, Forcheim, Germany). The acquisition parameters of abdominal CT protocol were used as listed in Table1. In this study, we aim to compare the benefits of using low kVp single energy and low keV VMI dual energy -CT acquisition in term of image quality and detectability based on clinical indication for hepatic lesion detection. The kVp values were varied from 70-120 kVp with 10 kVp interval and 120 kVp was defined as the reference kVp. For dual energy acquisition, three kVp-combinations were used: 80/Sn150, 90/Sn150, and 100/Sn150 kVp. The tube current modulation was activated to take account for elliptical shape of phantom in abdomen CT. The volumetric dose index ($CTDI_{vol}$) for 32 cm body phantom of each imaging protocol was recorded both for single and dual energy acquisitions.

The phantom was scanned 3 times for each acquisition and reconstructed into axial images using advanced modeled iterative reconstruction (ADMIRE) with strength 2. The standard soft tissue reconstruction kernel (Br36 for SECT and Qr36 for DECT) was used with the slice thickness of 0.6 mm and reconstruction field of view (FOV) fit to the scanned phantom of 320, 360 and 420 mm for small, medium, and large phantom size respectively.

Table 1 Acquisition and reconstruction parameters for abdomen single and dual energy CT protocols.

Acquisition mode	Single energy (SE)	Dual energy (DE)		
kVp setting	80, 90, 100, 110, 120	80/Sn150	90/Sn150	100/Sn150
Tube current modulation	On	On		
Quality reference mAs (A/B)	300	500*/250	350*/250	3600*/150
Rotation time	0.5	0.5		
Pitch	0.6	0.6		
Slice acquisition	192x0.6 mm	128x0.6 mm		
Reconstruction method	ADMIRE (2)	ADMIRE (2)		
Reconstruction Kernel	Br 36	Qr 36		

Note: For DECT acquisition, Quality reference mAs was adjusted only for tube "A", tube "B" was automatically computed by the system.

The reconstructed images of low- and high- kVp from DECT data were transferred to Syngo.via software, Siemens, Healthineer. The virtual monochromatic images (VMI) were generated at 40, 50, 60, and 70 keV using the "Monoenergentic+" function which is based on the image-based algorithm in Syngo Dual Energy application.

C. Task-based image quality assessment

In this study, the task-based image quality was assessed by using the imQuest software, version 7.1, designed by Duke Clinical Imaging Physics Group (Duke University).[9] The software assessed spatial resolution using the task transfer function (TTF), noise magnitude and texture using the noise power spectrum (NPS), and to estimate the ability of radiologist to detect specific lesions by using detectability index (d'). The specific clinical task in this study is to detect the small hepatocellular carcinoma (HCC) which is the hyperattenuating lesions in liver.

The TTF was assessed by placing the circular ROI on 20 mm hyperdense liver nodule in phantom image (Figure 1b). According to the methodology, 5 consecutive slices of axial image were used to compute the edge spread function (ESF) and then line spread function (LSF). Finally, by taking the Fourier Transform (FT) of LSF, TTF curve can be carried out.[9] Like the modulation transfer function (MTF), TTF curves can be summarized by the spatial frequencies at which the TTF reaches 50%, denoted as f_{50}.

The NPS was computed by placing four-square ROIs on the uniform area of liver region in phantom images (Figure 1c). The NPS curve was generated with the following equation[11]

$$NPS_{2D}(f_x, f_y) = \frac{\Delta_x \Delta_y}{L_x L_y} \frac{1}{N_{ROI}} \sum_{i=1}^{N_{ROI}} |FT_{2D}\{ROI_i(x,y) - \overline{ROI_i}\}|^2$$

where Δ_x and Δ_y are the pixel sizes in the x- and y-dimension, L_x and L_y are the ROI's lengths in pixel for both x- and y-dimensions, N_{ROI} is the number of ROIs used, $(\overline{ROI_i})$ is the mean pixel value averaged from $ROI_i\ (x,y)$. The NPS curves obtained from the measurement were used to quantify the noise magnitude by taking a square root of the area under the NPS curve, the noise texture by reporting the peak frequency, f_p, and the average NPS spatial frequency, f_{av}.

Combining the resolution (TTF) and noise (NPS) properties of the image with the predefined clinical imaging task (W) together, the detectability index (d') was then computed. The detectability index based on non-prewhitening observer model with eye filter (d'_{NPWE}) was computed for a predefined clinical task as follows:

$$d'^2_{NPWE} = \frac{[\iint |W_{task}(u,v)|^2 \cdot TTF^2(u,v) \cdot E(u,v)^2 dudv]^2}{\iint |W_{task}(u,v)|^2 \cdot TTF^2(u,v) \cdot NPS(u,v) \cdot E(u,v)^4 dudv}$$

where u and v are the spatial frequencies in the x-and y-directions, E the eye filter that models the human visual system sensitivity to different spatial frequencies, and W(u,v) the task function. The detection of small HCC task was assumed to represent the circular signal with a 15 mm diameter. The software computed the d' under the interpretation condition of 1.5 zoom factor and a viewing distance of 500 mm.

Results

Task-based image quality from images acquired for 70-120 kVp SECT and 40-70 keV-VMI acquired from DECT with varying the kVp combination; 80/Sn150,90/Sn150 and 100/Sn150 kVp were obtained for various size of phantom under tube current modulation as shown in Table 2. $CTDI_{vol}$ from each acquisition were collected for three phantom sizes and the values were shown in Table 3. The $CTDI_{vol}$ increased as the phantom size increased. The $CTDI_{vol}$ obtained from low kVp-SECT and the DECT scan mode were lower than that from a conventional 120 kVp scan in all phantom sizes.

Table 2 Summary of task-based image quality.

		SECT (kVp)						VMI-DECT (keV)				
		70	80	90	100	110	120		40	50	60	70
Small	Noise magnitude (HU)	20.09	20.27	19.78	19.84	20.04	18.56	80/Sn150	39.81	28.77	22.14	18.11
								90/Sn150	42.99	30.98	23.78	19.41
								100/Sn150	45.85	33.04	25.32	20.63
	$f_{av}(mm^{-1})$	0.22	0.22	0.23	0.23	0.22	0.23	80/Sn150	0.21	0.22	0.22	0.23
								90/Sn150	0.22	0.22	0.23	0.23
								100/Sn150	0.22	0.23	0.23	0.23
	$f_{peak}(mm^{-1})$	0.16	0.19	0.17	0.17	0.17	0.17	80/Sn150	0.11	0.17	0.17	0.17
								90/Sn150	0.11	0.19	0.20	0.20
								100/Sn150	0.16	0.16	0.16	0.16
	$f_{50}(mm^{-1})$	0.39	0.33	0.38	0.36	0.35	0.30	80/Sn150	0.22	0.22	0.22	0.23
								90/Sn150	0.27	0.26	0.27	0.27
								100/Sn150	0.23	0.25	0.27	0.28
	d'	49.80	43.82	41.64	38.72	35.21	40.88	80/Sn150	30.63	33.90	35.96	36.41
								90/Sn150	27.96	30.54	32.19	32.29
								100/Sn150	26.43	27.78	30.35	30.56
	CNR	5.78	4.91	4.74	4.38	4.13	4.55	80/Sn150	5.04	5.05	4.87	4.68
								90/Sn150	4.41	4.41	4.32	4.20
								100/Sn150	4.51	4.00	3.77	3.52
Medium	Noise magnitude (HU)	22.73	23.75	23.97	24.69	24.56	24.41	80/Sn150	47.69	34.38	26.44	21.55
								90/Sn150	51.08	36.54	27.82	22.55
								100/Sn150	52.67	37.73	28.74	23.27
	$f_{av}(mm^{-1})$	0.20	0.21	0.22	0.22	0.22	0.22	80/Sn150	0.20	0.21	0.21	0.21
								90/Sn150	0.20	0.21	0.22	0.22
								100/Sn150	0.20	0.21	0.22	0.22
	$f_{peak}(mm^{-1})$	0.14	0.16	0.17	0.16	0.17	0.17	80/Sn150	0.08	0.09	0.14	0.16
								90/Sn150	0.06	0.16	0.16	0.16
								100/Sn150	0.08	0.16	0.16	0.17
	$f_{50}(mm^{-1})$	0.31	0.31	0.30	0.35	0.34	0.33	80/Sn150	0.22	0.23	0.23	0.24
								90/Sn150	0.20	0.21	0.21	0.22
								100/Sn150	0.19	0.19	0.20	0.20
	d'	35.80	31.50	33.21	32.41	27.35	29.81	80/Sn150	17.14	18.94	22.19	22.00
								90/Sn150	18.09	19.85	21.34	21.36
								100/Sn150	21.79	25.35	29.35	30.69

Table 2 Summary of task-based image quality. (continued)

		SECT (kVp)						VMI-DECT (keV)				
	CNR	4.98	4.15	3.70	3.53	3.42	3.40	80/Sn150	3.38	3.29	3.40	3.22
								90/Sn150	3.53	3.39	3.22	3.04
								100/Sn150	4.40	4.25	4.08	3.89
Large	Noise magnitude (HU)	27.80	26.29	26.48	26.45	27.42	27.60	80/Sn150	52.54	37.73	28.82	23.41
								90/Sn150	56.07	39.98	30.30	24.43
								100/Sn150	57.15	40.74	30.86	24.85
	$f_{av}(mm^{-1})$	0.19	0.20	0.20	0.21	0.21	0.22	80/Sn150	0.18	0.19	0.20	0.20
								90/Sn150	0.19	0.20	0.20	0.21
								100/Sn150	0.18	0.19	0.20	0.21
	$f_{peak}(mm^{-1})$	0.13	0.14	0.14	0.14	0.16	0.17	80/Sn150	0.06	0.09	0.16	0.16
								90/Sn150	0.06	0.08	0.14	0.14
								100/Sn150	0.06	0.06	0.13	0.13
	$f_{50}(mm^{-1})$	0.30	0.26	0.27	0.32	0.25	0.25	80/Sn150	0.22	0.22	0.23	0.25
								90/Sn150	0.06	0.08	0.14	0.14
								100/Sn150	0.06	0.06	0.13	0.13
	d'	23.89	25.39	21.61	19.82	19.73	20.30	80/Sn150	12.05	13.94	15.69	16.22
								90/Sn150	15.59	16.51	18.74	19.38
								100/Sn150	11.52	14.13	17.49	20.34
	CNR	3.78	3.51	3.10	2.94	2.34	2.48	80/Sn150	2.83	2.88	2.86	2.71
								90/Sn150	3.54	3.31	3.39	3.31
								100/Sn150	2.99	3.09	3.17	3.26

*Note: *NPS, TTF at 50% (f_{50}), d' and conventional image quality metric (CNR), obtained from the images acquired for 70-120 kVp SECT and 40-70 keV-VMI from DECT with varying the kVp combination; 80/Sn150, 90/Sn150, and 100/Sn150 kVp in small, medium, and large phantom.*

Table 3 Radiation dose from different kVp in SECT and different kVp combination in DECT scan for small, medium, and large phantom size is displayed in $CTDI_{vol}$ (mGy).

	Single Energy						Dual Energy		
	120 kVp*	70 kVp	80 kVp	90 kVp	100 kVp	110 kVp	80/Sn150	90/Sn150	100/Sn150
Small	**10.44**	8.98	8.56	8.53	8.57	8.41	8.79	8.46	8.26
Medium	**14.45**	12.36	12.98	12.85	12.68	12.5	12.48	12.5	13.38
Large	**20.31**	17.62	16.93	16.85	16.4	16.43	17.04	17.3	18.11

A. Task transfer function (TTF)

For SECT acquisition, as the kVp is increasing, f_{50} shifted toward the lower frequency in small and large phantom sizes and shifted toward the higher frequency in medium phantom size. For DECT acquisition, f_{50} shifted to higher frequency as energy level of VMI increased in all kVp-combinations. The higher of f_{50} was observed in low kVp in SECT image compared to low keV- VMI in DECT for all phantom sizes where to be found at 70 kVp-SE in small phantom and at 100 kVp-SE in medium and large phantom. With increasing the phantom size, f_{50} shifted toward a lower frequency at low kVp-SECT (70-110 kVp). The shift of f_{50} toward to lower frequency as increased the phantom size was also founded in low energy VMI-DECT at 90/Sn150 and 100/Sn150 kV combination while the f_{50} remains constant for all phantom sizes in VMI images generated from 80/Sn150 kVp scan. The resulting lesion to liver background contrast in HU from different scanning condition was also displayed. Then compared to 120 kVp SECT, lesion contrast gradually improved as reduced the kVp in SECT while it was dramatically improved at low keV VMI in DECT especially at 40- and 50-keV in all phantom sizes.

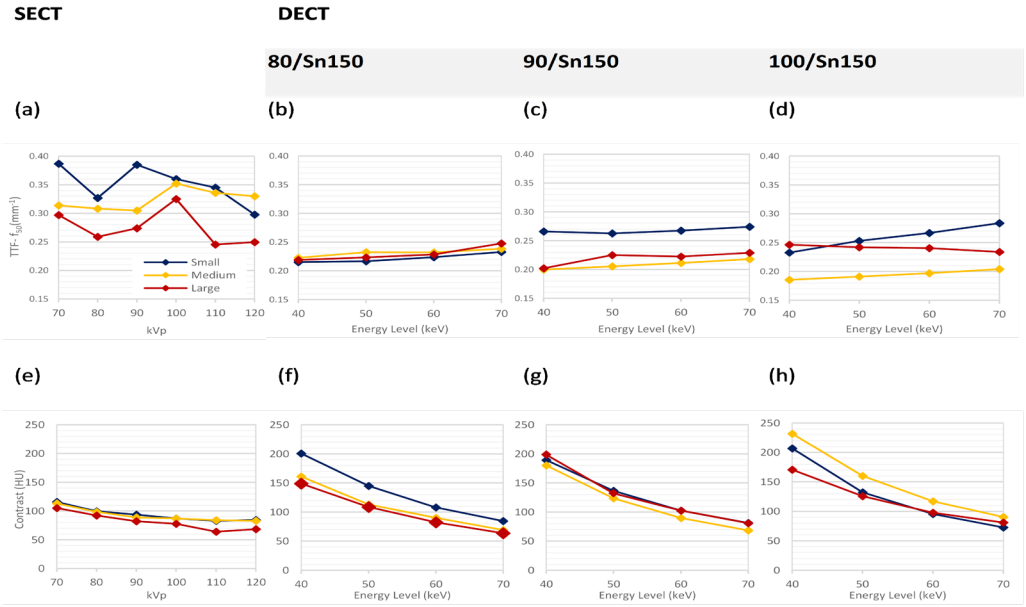

Figure 2 *The 50% TTF values and contrast in HU obtained from different scanning conditions for SECT and DECT acquisitions for small ,medium and large phantom. The top row is 50% TTF (f_{50}) values for (a) 70-120 kVp-SECT scan and for the 40-70 keV images from (b) 80/Sn150, (c) 90/Sn150 kVp and (d) 100/Sn150 kVp combination. in DECT scan. The bottom row is contrast (HU) values for (e) 70-120 kVp-SECT scan and for 40-70 keV images from (f) 80/Sn150 kVp,(g) 90/Sn150 kVp and (h) 100/Sn150 kVp combination in DECT scan.*

B. Noise power spectrum (NPS)

The noise magnitude (HU) increased with increasing the phantom size, however it remained constant in all kVp settings of SECT within a same phantom size. For VMI-DECT images, the noise magnitude gradually decreased by approximately 55% as energy level increased from 40 to 70 keV. The effect of kVp combination shown as an increased of noise magnitude (in all energy levels) as increased the kVp in low-kVp tube from 80/Sn150 to 100/Sn150. In term of the noise texture, the average NPS spatial frequency (f_{av}) shifted toward the lower frequency when reduced the kVp from 120- to 70-kVp or when increased the phantom size from small to large. In low keV-VMI generated from DECT scan, the f_{av} shifted toward the lower frequency when lowering of energy level from 70-to 40-keV and when the phantom size increased from small to large. The changing in of kVp combination slightly impact to the f_{av}, by the f_{av} was slightly increased as changing the kVp combination from 80/-to 100/Sn150 kVp as shown in Figure 3 (a-h).

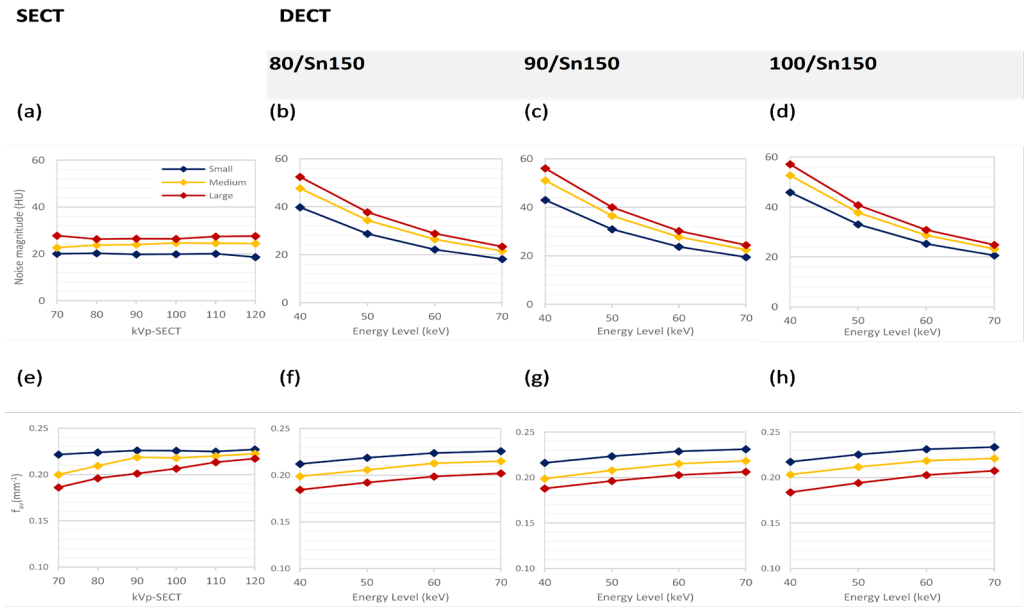

Figure 3 *Noise magnitude (HU) and average NPS spatial frequency (f_{av}) obtained from different scanning conditions for SECT and DECT acquisitions for small ,medium and large phantom. The top row is the noise magnitude (HU) obtained for (a) 70-120 kVp-SECT scan and for the 40-70 keV images from (b) 80/Sn150, (c) 90/Sn150 kVp, and (d) 100/Sn150 kVp combination in DECT scan. The bottom row is the average NPS spatial frequency (f_{av}) obtained for (e) 70-120 kVp-SECT scan and for 40-70 keV images from (f) 80/Sn150 kVp, (g) 90/Sn150 kVp and (h) 100/Sn150 kVp combination in DECT scan.*

C. Detectability index (d')

The detectability index (d') was computed based on the task of detection for 15 mm hyper-attenuation liver lesion.The d' estimated for images acquired using different kVp-SECT and low keV VMI-DECT, the obtained d' values were shown in Figure 4. The images obtained from low kVp-SECT scan at 70-, 80-, and 90-kVp yielded the higher d' compared to 120 kVp scan and d' decreased as phantom size increased. The highest d' was found for image obtained at 70 kVp for small and medium phantom size and at 80 kVp for large phantom size. On the contrary, as reduced the energy level from 70- to 40-keV of VMI in DECT, the d' decreased. At small phantom size, the d' was found to be highest at 80/Sn150 kVp compared to others. At the medium phantom size, the highest d' was found at 100/Sn150 kVp but at large phantom size, the highest d' was at 90/Sn150 kVp. Comparing between low kVp SECT and low keV-VMI DE scan, the d' was higher for low kVp-SECT scan in all phantom sizes.

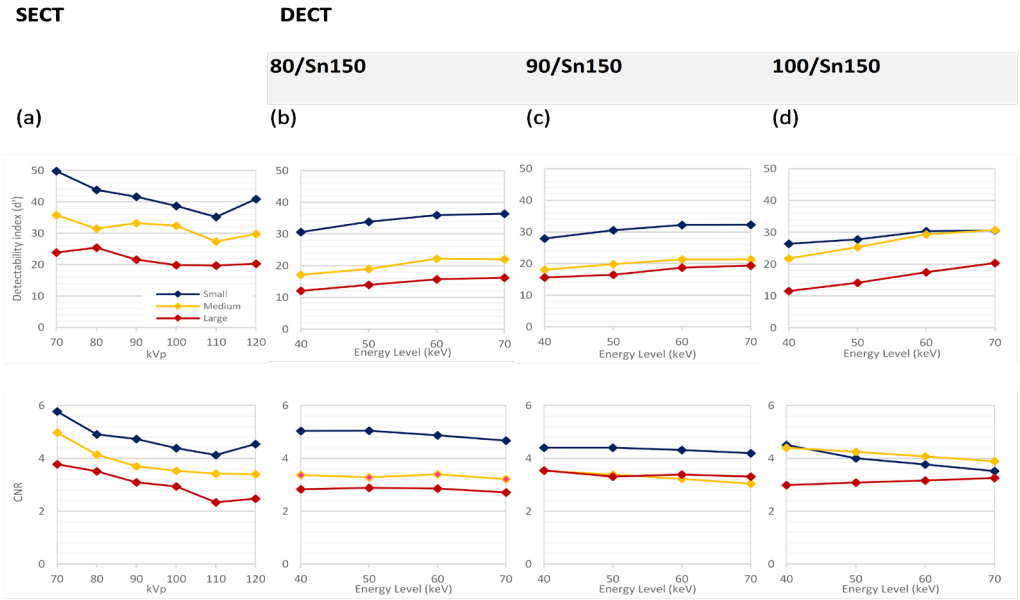

Figure 4 *Detectability index (d') and contrast to noise ratio (CNR) from different scanning conditions for SECT and DECT. The top row was d' values obtained from (a) 70-120 kVp-SE in all phantom sizes, the 40-70 keV images from (b) 80/Sn150, (c) 90/Sn150 and (d) 100/Sn150 kVp combination in DECT for small , medium and large phantom. The bottom row was CNRs obtained from (e) 70-120 kVp-SECT scan and for the 40-70 keV images from (f) 80/Sn150, (g) 90/Sn150 and (h) 100/Sn150 kVp combination in DECT.*

Discussion

This study performed to investigate the lesion detectability for small hepatic lesion in abdomen CT images acquiring at low kVp-SECT and low keV VMI-DECT on anthropomorphic liver nodules phantom under clinical protocol with tube current modulations. The clinical task in our study was defined as the detection of a 15 mm hyperattenuating hepatic lesion based on the typical lesion size that small HCC is usually detected in CT examination[7,12] and this size is in a range of clinically important to an effective treatment outcomes of HCC.[13,14] Our results demonstrated that the liver to lesion contrast (HU) was improved by reducing the kVp in SECT or by lowering the energy level (40-60 keV) of VMI in DECT according to increase of photoelectric interaction in low energy x-ray beam and complied with many studies.[5-7, 12] In this study the automatic tube current (mA) modulation was activated for all scanning protocols to take account with various sizes of phantom which the mA was modulated with the reference mAs at 120 kVp for standard patient size. Figure 3a demonstrated the excellent performance of the automatic mA modulation system in this scanner to maintain the image quality (noise) among the different kVp within the same phantom size. Therefore, the noise magnitude in this study was not affected by the kVp selection in SECT but for the synthetic images of VMI in DECT was not the same. The noise magnitude was dramatically increased as decreased the energy level of VMI especially at 40- and 50- keV for all phantom sizes. The impact of kVp combination shown as slightly increase of noise magnitude when increasing the kVp at tube "A" from 80 to 100 kVp. The f_{av} of NPS shifted toward the lower frequency imply to the shape of noise texture changed and demonstrated as image smoothness. In this study, the f_{av} shifted to the lower frequency was found in medium and large phantom sizes when reduced to lower kVp in SECT. This phenomenon was described by the study of Solomon *et al.* the manufacturer has implemented statistical weighting of the raw data into their iterative reconstruction algorithms which is more aggressive in low-signal condition (i.e., low dose or large phantom), the image will consist of slightly more low-frequency content and then visualized as larger grains compared to smaller phantom.[15]

The spatial resolution of images in this study was quantified using task transfer function (TTF). The further the TTF shifted toward lower frequencies, the larger spatial resolution reduction. For TTF, the circular edge technique had been used to plot the ESF and the ESF was influenced

by the image noise and the contrast between liver nodule inserted and liver phantom background, which these two are impacted as a function of kVp used in SECT or keV level of VMI in DECT as well as the kVp combination used and phantom size. Our study showed that the highest 50% TTF (f_{50}) was found at 70 kVp SECT in small phantom and at 100 kVp in SE in medium and large phantom corresponding to the high contrast and low noise settings.

The detectability index is a method of non-pre-whitening observer model with eye filter (NPWE) that incorporated the resolution, noise texture, diagnostic task, and 2D viewing conditions, changes of only one of these factors influenced the d'. The investigation of d' for various scanning conditions will be clinically benefit to the radiologist and technologist as guided for proper selection of scan and reconstruction parameters to achieve targeted diagnostic task on each examination. In our study, if the detection of 15 mm heperattenuation hepatic lesion was the primary diagnostic task, the scanning at 70 kVp-SECT is suitable for small and medium phantom and at 80 kVp-SECT for the large phantom size. Our result corresponds to the study of Hansan *et al*.[7] which reported higher lesion CNRs and higher radiologist preference scores in low kVp-SECT than that in 40-50 keV-VMI even though the lesion conspicuity (reflect to high lesion contrast) is high in low keV VMI-DE. However, if the dual energy acquisition is clinically required for small patient size, selection of 80/Sn150 kVp combination is most appropriate due to yielding the highest d' and 100/Sn150 kVp is preferred to improve the d' for larger patient. This was confirmed by the study of Michalak *et al*.[16] conducted for different phantom sizes .

This study demonstrated that using the low kVp SECT and low keV-VMI have potential on improvement of hepatic lesion detection in CT while reduce the radiation dose to patient compared to 120-kVp SECT scan. When compared the d' to 120 kVp scan, the higher d' values were mostly observed in low kVp SECT (70-100 kVp) rather than from low keV-VMI from DECT scan for all phantom sizes due to better image resolution and lower image noise in SECT images. However, at medium and large phantoms size, using 70 keV-VMI at 100/Sn150 resulting to comparable d'. This inferred that the utilizing the DECT in larger patient may add up the benefits on increase the diagnostic confidence to radiologist from additional image types generated from DECT data set such as virtual non contrast images (VNC), iodine images, iodine quantification, etc. without deterioration of lesion detection and dose penalty.

There are some limitations on this study which was carried out using the institutional abdomen imaging protocol at the standard acquisition scanning and single reconstruction parameter. The other parameters further from the kVp in SECT and keV combination in DECT along with various phantom sizes have not been investigated. Moreover, the variation on morphology of lesions (i.e., different lesion size or lesion contrast), have not been carried out. The hyperdense liver nodules in anthropomorphic abdomen phantom used in this study simulated the attenuation property of 90 HU liver nodule at 120 kVp scan, did not include iodine-based material, resulted in the deviation from the clinical study. However, this methodology has been accepted by multiple researchers who studied on d' of liver lesion in CT based on acrylic insert in image quality phantom.[17-20] To the knowledge from this study that the d' of low keV VMI is inferior to that from the low-kVp SECT acquisition, the further study should be conducted to study the impact of DECT parameters on d' that may help to improve the d' on VMI images in the future. The phantom study included more clinical lesions is required to add more information relevant to our results.

Conclusion

The lesion detectability for small hepatic lesion in abdominal CT images acquiring at low-kVp single energy and low keV VM image from dual energy acquisition were investigated. The highest d' was found at 70 kVp-SECT for small and medium phantom and at 80 kVp for large phantom. For SECT, reduced the kVp to 70- or 80-kVp improved the detectability index. For DECT, increased the energy level of VMI from 40-70 keV improved the d' in all phantom sizes. The kVp combination in DECT impacts the d' of VMI; at small phantom the d' values for each keV VMI was highest at image acquired from 80/Sn150 kVp and at larger phantom size, higher kVp on tube "A" is more favored.

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Conflict of interest

The authors have no relevant conflicts of interest to disclose.

Ethic approval

This study was performed on phantom, therefore this research was qualified with an exemption on the ethic committee approval.

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Development and psychometric properties of a questionnaire to measure the active aging index for older people

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ABSTRACT

Background: The world's aging is a global phenomenon. The active aging framework responds to this phenomenon by emphasizing on the connections between good health, participation, and security in the lives of older people.

Objectives: This study developed a novel measurement of active aging for older people by integrating the international concept with specific features of Thailand.

Materials and methods: Active aging measurement components were generated through relevant literature reviews, with content validity examined by experts. Internal consistency and test-retest reliability were used for examining measurement reliability. Two hundred older people living in Chiang Mai Province participated in a pilot survey.

Results: The active aging measurement was composed of four components including health, social participation, security, and enabling an environment for active aging. Good internal consistency was represented overall by Cronbach's alpha=0.77, while the test-retest reliability value was 0.89.

Conclusion: The active aging measurement was developed for older people. It is a valid and reliable measure of an active aging index.

Introduction

The speed of growth in the aging population is a global phenomenon. Thus, the World Health Organization (WHO) introduced "the policy framework of active aging" to promote active aging. Its concept describes the maintenance of positive subjective well-being, good physical, social and mental health and continued involvement in the family, peer group and community throughout the aging process.[1,2] This framework focuses on independence, autonomy, and quality of life. It is not only a broad concept of being healthy, but also recognition of factors that affect individuals and older populations. Despite the importance of active aging as a global policy concept, research into it has been limited for providing understanding of insights and associated perspectives.[2,3]

The active aging concept has been incorporated into policies that manage aging population worldwide, in Thailand. In examining the response to the active aging policy, the National Committee for the Elderly (NCE) of Thailand

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highlighted a special theme, according to dimensions of active aging in income security, impact from natural disasters, living arrangements and health.[4-6] The Active Aging Index (AAI) can serve as a baseline assessment to identify the potential of older people and monitor their progress.[7,8] From 2006 to 2020, the index of older people in Thailand was moderate, which correlates with many studies.[9-12] Studies have concluded that there is a need to improve the active aging level of older people in Thailand. Zaidi and Um analyzed an overall Asian AAI at the global level for monitoring, implementing, and evaluating policies, in which older people in Thailand needed to be directed for continued active engagement with the help of suitable employment opportunities for their age and health.[13]

The active aging policy provides a broader perspective that can be applied to effective strategies for older people to maintain a healthy lifestyle and active engagement in life activities. It is important to have a policy approach level to communities, and older people, and their families. The AAI is analyzed in many countries by selecting data sources and variables of AAI indicators.[14] While in Thailand, assessment on active aging has been developed by using a national indicator for constructing AAI.[9,10,15] Moreover, self-assessment has been developed for measuring the multidimensional attributes of active aging in a Thai context since 2014.[11] In 2017, the National Statistical Office of Thailand refined the initial formulation (health, participation, and security) further with the addition a fourth component to enable an environment for active aging as the fourth component. Therefore, this study aimed to develop a new questionnaire to measure the AAI according to a paradigm shift for achieving assessment at the individual level.[15]

Materials and methods

The active aging measurement questionnaire was created as follows: 1) it was comprehensive according to the WHO concept of active aging, indicators studied from various reference sources and the Thai context, and 2) it needed to be clear, concise, easy to understand, and without ambiguous/implicit language.

The first step of constructing this tool was to develop a first draft of the active aging measurement questionnaire, based on the conceptual framework of the WHO. In order to design a measurement, it was crucial to track progress of the United Nations Economic Commission for Europe, as introduced to the AAI in 2012. Thus, time limits were set for searching the database from 2013 to 2020. The literature from both the international and Thai measurements were reviewed by focusing on components and scales, selected for the Thai context. The active aging aspects were determined by studying components of the AAI indicator. The researchers studied components of the active aging framework mentioned in different books and research studies.

The second step, involved psychometric property testing, and content validity was investigated in the first draft by five experts, who had five years or more practical experience in the geriatric field. These experts consisted of two occupational therapists, one physician, one nurse and one social worker. After receiving feedback and recommendations from the experts, the Index of Item-Objective Congruence (IOC) was used in order to find content validity.[16] Then, the IOC index was analyzed and improved against the content of checklist items as a second draft, following advice from the experts. Due to it being a stable and easy-to-use tool for multidimensional insights, it realized the potential of older persons in the general situation. For preliminary psychometric testing, pilot testing was used to examine, based on the protocol of Ingersoll -Dayton, Kespichayawattana, and Saengtienchai.[17] The data were collected from one community by using convenience sampling. A default sample size of 30 participants was recommended for pre-testing.[18] Therefore, 35 participants were selected as subjects for this test by taking 15% of the member population (total number of members=232) at Community Club of Piyamal Center, Muang District, Chiang Mai Province. A think-aloud question was used to explore the perception of the participants. The researchers asked the older persons to consider each question one by one. Then, language in the second draft of measurement was improved according to recommendations from the older persons and used in the draft. The IOC was investigated in the final draft.

Then, internal consistency and test-retest reliability were used to examine measurement reliability. Participants: the inclusion criteria for the participants were as follows: 1) people aged 60 years and older, 2) member of the Community Club in of Nongpakrang Municipality, Mueng District, Chiang Mai Province, 3) ability to understand the questionnaire, and 4) voluntary participants with their informed consent to take part in this study and giving their informed consent to take part in this study. Data collection: the researchers contacted the community selected in the target area and collected the data. After that, the samples were selected using a proportional size (30 people) and convenience random sampling. Advertisements in the community invited its members to join this study. The participants were met to explain the details and purpose of this study to them, before describing the consent process. The data for time 1 and time 2 were collected. The researchers returned one week after the time 1. The participants were the same persons each time.

In the third step, a survey was performed with older people in Chiang Mai area, when the researchers contacted a selected community in the target area and collected the data. After that, samples were selected using a proportional size and systemaic random sampling. The sample used in this step was used following the protocol of Denscombe who recommended at least 200 subjects as an appropriate number in performing a survey.[19] Therefore, this test selected 200 participants. Older people living in Chiang Mai Province, Northern part of Thailand, were recruited in the study. In a data collection setting, District boundaries of Chiang Mai Province were classified into three categories: urban, suburban, and rural areas in order to represent the various characteristics of older people by using stratified sampling. One urban, one suburban and one rural area were selected from different districts of

Chiang Mai Province by using simple random sampling. In calculating each active aging dimension, (health, social participation, security and enabling an environment for active aging) a weighted score was used, and an index of each one was summed up by weighted score,[20] as shown in the formula below:

AAI = 1/4 (HI) + 1/4 (SPI) + 1/4 (SI) + 1/4 (EEI)

Then, the AAI was classified into three levels according to the Human Development Index (HDI), developed by the United Nations Development Programme.[20] It was constructed to measure the AAI level as follows:

Index score 0.000-0.499 is low level
Index score 0.500-0.799 is moderate level
Index score 0.800-1.000 is high level

Results

The components of active aging measurement between 2013-2020 from database (both the international and Thai) were found that WHO conceptual was primary used for building the index. The AAI was calculated on adjusting the flexible methodology on selection of appropriate data sources that the index preserved it core concept and structure. The AAI methodology uses several data sources (secondary data) from different sources depending on available statistical sources to capture various dimensions of active aging. For local purposes, the AAI was calculated by using the questionnaire. It is flexible tool that can apply the domains under concept of active aging to reflect the potential of older persons to the specific circumstances and purposes in their own contexts. There were some differences in details of indicators in each index component and grouping as summary in Table 1.

Table 1. Summary of some differences in details of components of active aging measurement.

Year	Authors	Country	Component	Indicators	Data collection for AAI
2013	Zaidi *et al.*[21]	EU Member States and some other European countries	Employment (national level)	Employment rate 55-59, employment rate 60-64, employment rate 65-69, employment rate 70-74	Review secondary data from different sources
			Participation in society	Voluntary activities, care to children/ grandchildren, care to older adults, political participation	
			Independent, healthy, and secure living	Physical exercise, access to health and dental care, independent living, relative median income, no poverty risk, no severe material deprivation, physical safety, lifelong learning	
			Capacity and enabling environment	Remaining life expectancy at age 55, share of healthy life expectancy at age 55, mental well-being, use of ICT, social connectedness, educational attainment	
2014	Thanakwang *et al.*[11]	Thailand	Being self-reliant	Living independent and being self-care in daily activities, having autonomy in decision making	Questionnaire : Validity = 0.91 Internal consistency reliability = 0.95 External reliability = 0.92
			Being actively engaged with society	Participating in social activities, connecting with friends, contributing to society	
			Developing spiritual wisdom	Making merits, being acceptance and calmness, trusting and practicing religious doctrines	
			Building up financial security	Preparing financially for later life and for funerary activities, having enough money for daily expenses	
			Maintaining a healthy lifestyle	Maintaining exercise, eating healthful food, managing stress, avoiding substance abuse	
			Engaging in active learning in active lifelong learning	Being physically and cognitively active, engaging in meaningful activities, engaging	
			Strengthening family ties to ensure care in later life	Strengthening family ties, teaching children about filial piety	

Table 1. Summary of some differences in details of components of active aging measurement. (continued)

Year	Authors	Country	Component	Indicators	Data collection for AAI
2014	Zasimova and Sheluntcova.[22]	Russia	Health	Chronic conditions, physical ability, pain and discomfort, mental health, physical health condition	Not available
			Participation in social activities	Work participation, community participation, family and friends participation	
			Security	Financial stability, living conditions, living security	
2015	Saengprachak-sakula.[20]	Thailand	Health	Physical, mental, visual ability, hearing ability, limitation in active in daily living: ADL, functional limitation	Review secondary data from different sources
			Participation	Member in social group, participating in social group	
			Security	Income adequacy, home ownership, living together in family	
2015	International Longevity Centre Brazil (ILC-Brazil).[7]	Brazil	Health	Physical and mental health, reducing health inequalities	Not available
			Lifelong learning	Equips to stay healthy, remain relevant and engaged in society, and assure personal security	
			Participation	Engagement in work (paid and voluntary) and any social, civic, recreational, cultural, intellectual, or spiritual pursuit that brings a sense of meaning, fulfillment and belonging	
			Security	the effects of climate change, natural disasters, disease epidemics, organized crime, human trafficking, criminal victimization and interpersonal violence and abuse, sudden and/or prolonged economic and financial downturns, risks can be disease, poverty and hunger, deaths in the family, periods of unemployment, and moving away from homeland	
2016	Lim and Thompson.[23]	Singapore	Health	Self-assessed health status, psychological well-being, disabilities, activity of daily living (ADL) limitations, functional limitations, exercise behavior	Review secondary data from different sources
			Participation	Participation in workforce, interaction with family members, participation in clubs/groups	
			Security	Sufficiency of income, source of income, house ownership, living arrangement, safety facilities	
2017	National Statistical Office Thailand.[15]	Thailand	Health	Self-reported health status, Self-reported happiness, engaging activity independently, visual ability, hearing ability, exercise	Review secondary data from different sources
			Participation	Employment, club/group participation, village/community participation, care to members in family	
			Security	Sufficiency of income, house ownership, living arrangement, safety facilities	
			Capacity and enabling of active aging	use of ICT, literacy	

Table 1. Summary of some differences in details of components of active aging measurement. (continued)

Year	Authors	Country	Component	Indicators	Data collection for AAI
2018	Guntupalli and Chakraborty.[24]	India	Employment	Employment rate 55-59, employment rate 60-64, employment rate 65-69, employment rate 70-74	Review secondary data from different sources
			Participation in society	Voluntary activities, care to children/ grandchildren, care to older adults, political participation	
			Independent, healthy, and secure living	Physical exercise, access to health and dental care, independent living, relative median income, no poverty risk, no material deprivation	
			Capacity and enabling environment	Remaining life expectancy at age 55, mental well-being, social connectedness, educational attainment	
2019	Nyqvist, Nygård and Snellman.[25]	Finland	Employment	Employment rate 55-59, employment rate 60-64, employment rate 65-69, employment rate 70-74	Questionnaire : not available psychometric property
			Participation in society	Voluntary activities, informal caregiving, political participation	
			Independent, healthy, and secure living	Physical exercise, financial security, physical safety, lifelong learning	
			Capacity and enabling environment for active aging	Self-rated health, mental well-being, use of ICT, social connectedness	
2019	Hus ***et al***.[26]	Taiwan	Employment (national level)	Employment rate 55-59, employment rate 60-64, employment rate 65-69, employment rate 70-74	Review secondary data: national, city, community, household, individual
			Participation in society	Voluntary activities, caring for children/ grandchildren, care to older adults/disabled relatives, political participation, other social group participation,	
			Independent, healthy, and secure living	Physical activity, access to health and dental care, independent living arrangement, relative median income, no poverty risk for older persons, no severe material deprivation for older persons, physical safety (from violence), lifelong learning, physical function independence, no severe cognitive impairment, no depressive symptoms, primary prevention care utilization, physical safety (from accidents or injuries), owning assets	
			Capacity and enabling environment	Remaining life expectancy achievement of 50 years at age 55, share of healthy life years in the remaining life expectancy at age 55, mental well-being, use of ICT (internet), social connectedness, educational attainment of older persons, transportation accessibility, transportation convenience, barrier-free space , social integration and social respect	

The active aging measurement was finalized into 4 components: health, social participation, security and enabling an environment for active aging. The first draft of measurement for active aging consisted of 28 items in the four performance components, including health (14 items), social participation (4 items), security (7 items), and enabling an environment for active aging (3 items). The result of IOC from the experts was between 0.6 and 1.00. To ensure that the participants could understand the questions clearly, they were asked to express their own perception. Then, the characteristics of questions were clarified, and examples provided for easy understanding. After these improvements, the IOC was investigated. A number of items in health (2) and enabling an environment for active aging (1) was decreased to leave a total of 25 from 28 in the final version, due to those three making a similar point. The IOC of the final version was between 0.9-1.0 (Table 2).

Cronbach's alpha coefficient of measurement with four domains of 0.77 was interpreted as acceptable,[27,28] as shown in Table 3.

The final version evaluated stability. The Pearson correlation coefficient was 0.89, which interpreted as good,[29] as shown in Table 4.

Two hundred participants were evaluated in the AAI by using the new active aging measurement. The characteristics of the study population are described in Table 5.

Table 2. Measurement components of active aging and IOC between the first draft and final version.

Components	Indicators	First draft		Final version	
		Number of items	IOC	Number of items	IOC
1. Health	H1. Chronic condition	2	0.5-1.0	1	1.00
	H2. Pain & discomfort	2	0.5-1.0	1	1.00
	H3. Physical ability	5	0.8-1.0	5	0.9-1.0
	H4. Mental health	2	0.8-1.0	2	1.0
	H5. Physical health condition	3	1.0	3	1.0
2.Social participation	SP1. Religion	1	1.0	1	1.0
	SP2. Community	2	0.8-1	2	1.0
	SP3. Family & friends	1	1.0	1	1.0
3. Security	S1. Financial stability	2	0.8-1	2	1.0
	S2. Living conditions & security	5	0.8-1.0	5	0.9-1.0
4. Enabling an environment for active aging	E1. Use of ICT	1	1.0	1	1.00
	E2. Literacy	2	0.5-1.0	1	1.00
Total		28	0.6-1.0	25	0.9-1.0

Table 3. Internal consistency reliability of the active aging measurement.

Components	Number of items	Cronbach's Alpha	Interpretation
1. Health	12	0.77	Acceptable
2. Social participation	4	0.72	Acceptable
3. Security	7	0.79	Acceptable
4. Enabling an environment for active aging	2	0.76	Acceptable
Total	25	0.77	Acceptable

Table 4. Reliability test of the active aging measurement.

Components	Number of items	Pearson's Coefficient	Interpretation
1. Health	12	0.91	Excellent
2. Social participation	4	0.90	Excellent
3. Security	7	0.96	Excellent
4. Enabling an environment for active aging	2	0.51	Poor
Total	25	0.89	Good

Table 5. Socio-demographic characteristics of the participants.

Variables	Frequency (n=200)	Percent (%)
Gender		
Male	39	19.50
Female	161	80.50
Age (yrs.)		
60-70	147	73.50
71-80	46	23.00
81 over	7	3.50
Religion		
Buddhism	200	100.00
Marital status		
Single	15	7.50
Married	109	54.50
Divorce	32	16.00
Widowed	44	22.00
Educational level		
Uneducated	6	3.00
Less than high school	113	56.50
High school graduate	44	22.00
College	17	8.50
Graduate and higher	20	17.00

The attributions of active aging among the Thai older persons in the community are shown in Table 6. Mean score among the AAI was at the moderate level.

Table 6. Frequency and percentage of the older persons, classified by the active aging level.

Active aging level	Frequency (n=200)	Percent (%)	Active aging index		
			Min	Max	±SD
High	32	16.00	0.80	1.00	0.82±0.04
Moderate	168	84.00	0.68	0.77	0.77±0.03
Low	0	0	0	0	0
Total	200	100	0.68	1.00	0.77±0.03

Discussion

The aim of this study was to develop a measurement for identifying the AAI at the individual level. The new measurement attempted development within the Thai context so that older people would find it simple to use and easy to understand. This measurement could be assumed as appropriate for use by older persons because its contents of items were improved by using their perspective in the Thai context. Moreover, the new measurement was intended to apply in the community context. The United Nations Economic Commission for Europe (UNECE) suggested that the AAI can be adjusted in various contexts for local purposes.[14]

The four components (health, social participation, security and enabling an environment for active aging) of measurement were identified within the concept of active aging (WHO)[1,7,8] at the national level and in Thai contexts, [2-5,10,11,15] in order to measure the reviewing stage of at the source of data. In Thailand, the concept of active aging in the Thai context of older persons was reported at the national level in 2017[5] and National Statistical Office report,[15] which led to Thai older persons actively. Thus, this measurement was developed in the Thai context for further study in promoting active aging in the community. The development of new assessments, in accordance with the context has been increased according to the purpose of use. [8,27]

This study demonstrated that the psychometric properties of the active aging measurement questionnaire showed desirable validity and reliability. The quality of content validity of in this measurement was based on the IOC and findings from the five experts in this field. The items were revised and three removed. Three items were deleted due to vague and duplication. The question in this measurement was congruent with exploring the perception of older people. The final version of measurement had the IOC of 0.9-1.0, thus reaching a high level of value.[16] Internal consistency of the active aging measurement was 0.77, based on Cronbach's alpha coefficient, indicating good internal consistency reliability as health is a main pillar of active aging.[28] To ensure the consistency of results over time, the coefficient of a person was 0.89 in total, indicating good stability. Moreover, the measure of internal consistency reliability of each component domain, indicated poor to excellent stability and reliability, ranging from 0.51-0.96.[29] On the other hand of this study, the Cronbach´s Alpha value (0.95) and Person correlation coefficient reliability (0.92) were lower than Thanakwang *et al*.[11] However, the active aging measurement is a valid and reliable questionnaire.

Based on the component factors, AAI (ranges from 0 to 1) has been calculated. In this study found that mean AAI of the total was 0.77, active aging level had at moderate level, same as the previous studied.[9,14,29] The AAI can be used as a tool to monitor the change for implementation based on the component factors for individual life balance, being an individual checklist of possible social and economic activities and capabilities. The concept of active aging has been already recognized as particularly profiles that for more favorable age actively.[12, 30, 31] AAI is one factor to achieve Sustainable Development Goals (SDGs) in Thailand as a relatively new philosophy to improve human well-being as a development goal.[32,33] Therefore, the many factors; physical, mental, social, enabling factors to pay attention and emphasize to be a great relevant for active aging. In this way, the new active aging measurement can assess active aging levels, and their determinants can use to enabling the design and implementation of clinical and public health interventions to optimize and promote healthy aging.

Conclusion

We developed a new measurement to assess AAI

to adopt and implement at individual level at community. The active aging measurement comprised 25 items of four components and has satisfactory validity and reliability for assessing active aging levels to promote active aging. We believe that the development of this scale will make it possible to move forward the service to induce, enable the design and implementation of interventions to rise aging society of communities in Thailand.

Limitations and suggestions

The researchers intend to mention some limitations, this study was not conducted in a nationally representative sample covering all geographic regions of Thailand. It was a study of the elderly living in Chiang Mai or Northern Thailand. Moreover, it has been applied for questionnaire development only older people in community who were social-bound elders. The sample size used in the study to validate the AAI was relatively small, it was not nationally representative of the other areas of Thailand. Therefore, further studies should expand to validate with larger and representative samples the other contexts. For future developmental steps of the measure these differences (bed-bound and home-bound elders) will be further examined. Another limitation is that this measure of active aging levels has been applied only to Thai elders in community context. This measure should be used in cross-cultural research conducted in other Asian and non-Asian countries.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethic approval

This study was approved by the Ethics Committee of the Faculty of Associate Medical Sciences, Chiang Mai University (number: AMSEC63EX040).

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Developing a PET normal brain template using diffusion tensor imaging images: A proof of concept

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ABSTRACT

Background: Registered Positron emission tomography (PET) brain images to the standard normal PET brain templates can be performed to diagnosis dementia by using a vendor software, in which the brain template is based on T1-Weighted (T1W) images. However, the imperfection of an overlap between PET images and the PET-T1W based brain template could be observed.

Objectives: This pilot study aimed to develop a new PET brain template and compare the accuracy of image registration between a conventional PET-T1W based brain template and our proposed PET-DTI based brain template.

Materials and methods: The new PET-DTI based brain template was developed from twenty-four normal volunteers (age ranged 42-79 years old) who underwent 11C-Pittsburgh compound B PET scans and both T1W and diffusion tensor image (DTI) magnetic resonance imaging brain scans. The correction of Eddy-Current distortions and related artifact removing in DTI images were performed using the open-source FMRIB Software Library (FSL) to generate whole-brain probabilistic tractography maps (MRI-Probtract). MRI-Probtract map was then deformably registered and normalized to PET images, which were used for brain boundary guidance. The accuracy of image registration was assessed by applying the newly developed PET-DTI brain template to PET images of four mild cognitive impairment patients who underwent the same brain-scanning protocols. The accuracy of image registrations using the conventional PET-T1 and PET-DTI templates was evaluated qualitatively by three nuclear medicine physicians. Wilcoxon Signed Ranks test was used to compare registration scores of the two methods. Additionally, the dice similarly coefficient was obtained to quantitatively evaluate the accuracy of image registration.

Results: The registration scores of the PET images registered with the PET-DTI template were significantly higher than the PET-T1 template at p-value < 0.05. This result is consistent with the dice similarly coefficient where the value of PET-DTI template was higher.

Conclusion: Result of this pilot study showed that new PET-DTI brain template provides higher registration quality, suggesting the feasibility of using PET-DTI template in a clinical PET study of the brain.

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Introduction

Positron Emission Tomography (PET) is an imaging device in nuclear medicine to detect lesions inside the human body. After a small injection of sufficient amounts of radiopharmaceuticals into a patient's body, the radiation compounds bind with the target organ. Images can then be taken by imaging devices, such as PET-Computed Tomography (PET-CT).[1,2] Clinically, nuclear medicine radiologists interpret visual PET images qualitatively by abnormal uptake or non-uptake of radiopharmaceutical substances in the area of interest. Besides, quantitative analysis is performed by calculating numerical values from such area. The standard uptake value (SUV) indicates the ratio of radioactivity concentration in tissues by patient's body weight. Normally, the SUV value is high at the area of high uptake of radiopharmaceuticals.[3-5]

Development of qualitative analysis is especially important for patients with specific pathologies, including brain atrophy. It helps to reduce visual errors at the brain region in which radiopharmaceutical uptakes. Therefore, qualitative analysis is widely used to interpret patient's lesions. For example, to diagnose brain function in particular dementia using PET images, a standard PET brain template is required for referencing radiopharmaceutical uptake values at a voxel level of normal brain. It is typically developed from a group of subjects with intact memory. The normal pattern of radiopharmaceutical uptake at different brain regions was used as a reference for diagnosing brain function abnormality. This standard template is overlaid on PET images to detect an increase or a decrease of radiopharmaceutical uptake at any brain regions.[6-8]

Currently, registering PET images to the standard PET brain templates can be performed using a vendor software, in which the brain template is based on T1-weighted magnetic resonance imaging (MRI). However, the imperfection of an overlap between PET images and the PET-T1W based brain template could be observed. The image of cerebral cortex from an aging person especially in brain atrophy or hydrocephalus has less details than the image from a healthy person. These anatomical changes in brain cortex on T1W images can cause discrepancies between PET brain image and PET-T1W based brain template, leading to wrong interpretation.[9,10] Therefore, PET-T1W based brain template requires an improvement. The T1W image of the brain could be replaced by diffusion tensor imaging (DTI) MRI. The DTI map represents fiber tract orientation of white matter of the brain, which is profoundly less affected by brain atrophy than gray matter.[11] In this study, we hypothesis that utilizing DTI map to develop brain template could improve the accuracy of image overlay between PET image and brain template in the case of diagnosing spatial brain function abnormality compared with the vendor's standard template. The potential use of DTI based brain template in solving miss-interpretation around the edge of the cerebral cortex in animal's brain model and human brain model has also been reported. [12,13]

In this study, we aimed to (1) develop a new PET-DTI based brain template, and (2) validate our method by comparingour brain template with the standard template derived from normal brain volunteers and comparing the accuracy of image registration between PET images and both templates in dementia patients with deteriorated pathology of brain tissue.

Materials and methods

This was a retrospective study. We collected PET/CT and MRI images from a group of volunteers enrolled in the "Assessment of the Accumulation of Amyloid and Tau proteins in Thai People without Degenerative Brain Disease" project, National Cyclotron and PET Centre, Chulabhorn Hospital, Thailand. The method consists of two parts. First, two types of brain templates: PET-DTI and PET-T1W were created as a part of method development. Second, registration accuracy of two different templates was evaluated and compared after registering each template with four dementia participants, which were part of method validation. This study was approved by the Human Research Ethics Committee of Chulabhorn Research Institute.

Participants

PET/CT and MRI images of twenty-four normal healthy participants during 2016-2017 (age ranged 42-79 years old) were collected. All were participated in the "Assessment of the Accumulation of Amyloid and Tau proteins in Thai People without Degenerative Brain Disease" project, National Cyclotron and PET Scan Centre, Chulabhorn Hospital. Also, PET/CT and MRI images of four dementia participants who met our inclusion criteria were retrospectively to validate a new PET template. The inclusion criteria included male and female patient being diagnosed of dementia and being able to participate in MRI scan. Healthy volunteers and patient were scanned using identical PET/CT and MRI protocol. Patients who could not finish both PET/CT and MRI scan were excluded.

MRI imaging procedure

MRI imaging was performed on the Siemens/Trio 3.0 Tesla MRI scanner (Siemens Healthcare, Erlangen, Germany). A 3D sagittal T1-wieghted sequence was first obtained (slice thickness =1.0 mm with 50% overlap, Repetition Time (TR) =1600 msec, Time to Echo (TE) =2 msec, flip angle =90°, and matrix size =256x256 pixels). Then a whole-brain single shot echo planar imaging (EPI) pulse sequence was applied for DTI image data using following parameters: slice thickness =2.0 mm, TR =6508 msec, TE =90 msec, flip angle =90°, number of averages =1, voxel size =1.95x1.95x2 mm, matrix size =128x128 pixels, and direction =64.

PET imaging procedure

PET imaging was conducted on the Siemens/Biograph16 PET/CT scanner (Siemens Healthcare, Erlangen, Germany) with 3D mode. A radioactive rod source of 68Ge was used for daily quality control. CT brain images for localization and attenuation correction was performed. The PET dynamics protocol was done immediately after

intravenous injection of 555 MBq 11C-PiB (PET scan time: 70 mins, matrix size: 168, zoom: 1, and a Gaussian filter with a full width at half-maximum: 5.0). The images were reconstructed using a fully 3D ordered subset expectation maximization (3D-OSEM) algorithm for all corrections (scatter, random, dead time, attenuation, and normalization) with 4 iterations, 8 subsets, and a 4 mm pixel size. The scan time ranged from 50 to 70 mins.[14-16]

Developing of PET brain template

The template using the same method as Chotipanich *et al* was created.[17] PET-DTI brain templates were constructed using the scan of twenty-four normal participants. All participants completed three scans: PET, MRI-T1W, and MRI-DTI. The PET-DTI brain template was generated by averaging individual PET images of normal brains, which had their DTI images coregistered to the template and spatial normalized. This template represents the sampled-basedspatial pharmaceuticals uptake in normal brain. The details of data processing were elaborated as follows:

[I.] All PET and MRI images in DICOM format (Digital Imaging and Communications in Medicine) were converted to NifTI format (Neuroimaging Informatics Technology Initiative) using MRI Convert software.[18]

[II.] The prepared DTI images was imported to FMRIB Software Library (FSL) for preprocessing and modeling processes. Firstly, Brain Extraction Tool (BET) was used for removing the skull while retaining only brain tissue (line estimate: 0.15 and intensity: 0.10). Secondly, FMRIB's diffusion toolbox (FDT) was used for Eddy current correction, local modelling of diffusion parameters, tractography and connectivity-based segmentation, and local fitting of diffusion tensors. Finally, a whole-brain probabilistic DTI tractography map (MRI-Probtract) was obtained.[19]

[III.] For PET images, SPM 99 software (distributed under General Public License as published by the Free Software Foundation) was used for the entire construction process. Anterior commissure (AC) area was set as a reference anatomical landmark to reorient PET and MRI-Probtract images to the same position. After this process, the reoriented slices of PET and MRI-Probtract images were arranged for image registration (rPET images).

[IV.] SPM 2 software (distributed under General Public License as published by the Free Software Foundation) was used for co-registration of the group (twenty-four participants) data. Each individual B0 image obtained during the DTI image processing was co-registered to rPET image data. The output was subsequently normalized with MRI-Probtract. Finally, the new PET-DTI brain template was obtained.

For the development of PET-T1W brain templates, the same data processing technique was performed as mentioned above, except that we replaced the DTI with T1W in each step to obtain another PET-T1W brain template (Figure 1).

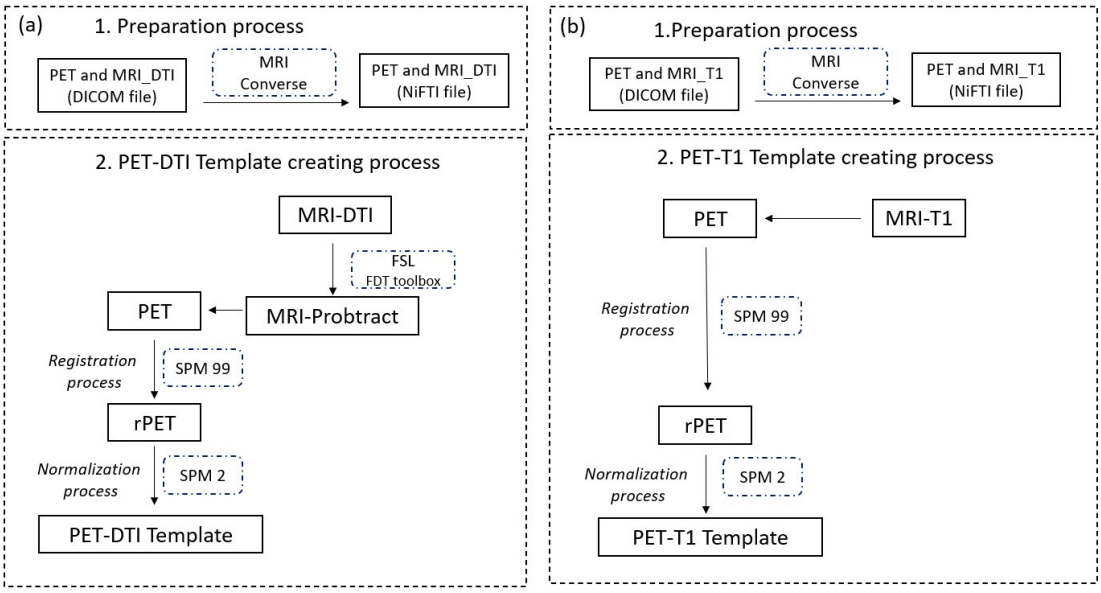

Figure 1 *Comparison between development process of proposed PET-DTI brain template (a) and the standard PET-T1 brain template (b) of normal brain.*

Image registration quality assessment in four dementia patients

The newly developed PET-DTI brain template and the conventional PET-T1W brain templates were registered to PET images of four dementia patients. The dice similarity coefficient score (DSC) was assessed to measure the quality of image registration for both methods. The lateral ventricle area in templates and PET brain contouring were drawn by using ImageJ software to calculate dice score as shown in Figure 2. The value of a DSC ranges from 0, no spatial overlap between two images, to 1, perfect overlap. The DSC score was defined as follow:

$$DSC = 2 \times |X \cap Y| / (|X| + |Y|)$$

Where X and Y are the region of interest in two PET template and PET images, respectively. ∩ represents the intersection operator. |X| is the area of X, and |Y| is the area of Y.

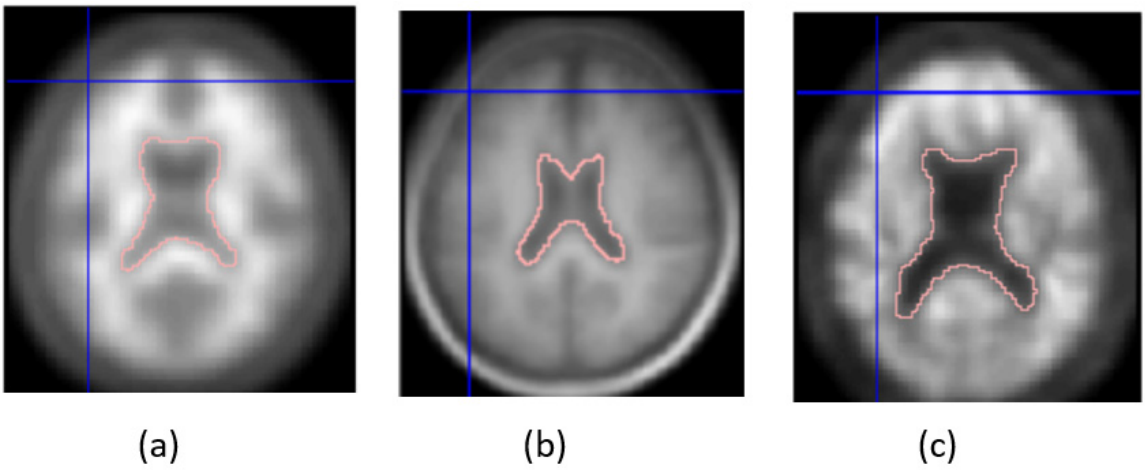

Figure 2 *Comparison of lateral ventricle segmentation between proposed PET-DTI brain template (a), standard PET-T1 brain template (b), and PET image(C) of normal brain in the same patient. This segmented area was used to calculate the DSC score for comparison between methods.*

Accuracy scores of image registration measurement by nuclear medicine radiologists

Although DSC is among the widely used methods for assessing image registration quality, it does not provide the accuracy of spatial information inside the image area. Therefore, the accuracy of PET image and templates registration using human visual inspection was assessed by slice-by-slice approach. The accuracy scores of images overlay between the developed method (PET image/PET-DTI based template registration) and the standard method (PET image/PET-T1W based template registration) were assessed by three nuclear medicine radiologists with more than five years of experience in the PET-CT interpretation. Blind observations were performed. The radiologists scrolled through all slices of PET image and examined each slice to evaluate the overlap between the PET images and the brain template and provides the overlapping scores between PET image and PET brain template at eight areas: four at the outer edge and four at the inner edge of cerebral cortex as shown the example of evaluation in Figure 3. Four areas at the outer edge of the cerebral cortex are right inferior frontal gyrus (A), left inferior frontal gyrus (B), right Lateral cerebral sulcus (C), and left Lateral cerebral sulcus (D). Four areas at the inner edge of the cerebral cortex are right anterior horn of lateral ventricle (E), left anterior horn of lateral ventricle (F), right posterior horn of lateral ventricle (G), and left posterior horn of lateral ventricle (H) as shown in Figure 4. The given registration scores are based on how PET image was overlapped with brain template using the assessment criteria as follow: 3 for perfect overlapped, 2 score for partially overlapped, and 1 for non-overlapped.

The scores from all nuclear medicine radiologist were used to compare between our developed and the standard template.

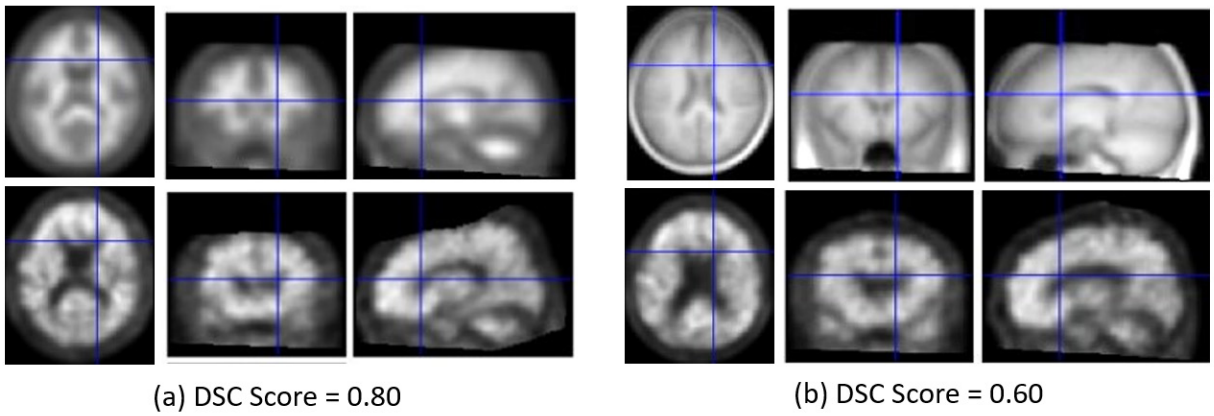

Figure 3 *Shows an example of brain-region localization at a reference point F (crosshair) and the accuracy of lateral ventricle overlapping using DSC score in patient 1. (a): proposed PET-MRI brain template in upper row and PET image in lower row, (b): standard PET-T1 brain template in upper row and PET image in lower row (b). Accuracy of lateral-ventricle area overlapping (DSC score =0.8) in proposed PET-MRI showed more improvement compared to the standard method (DSC score =0.60).*

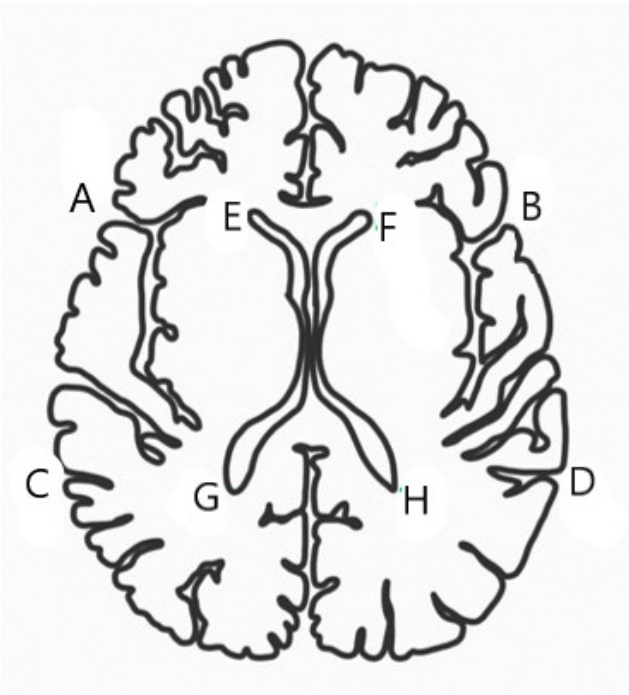

Figure 4 *Reference brain regions, including four areas at the outer edge of the cerebral cortex (A-D), four areas at the inner edge of cerebral cortex (E-F-G-H), were used to evaluate the image registration scores.*

Statistics and data analysis

The similarity between PET images and both brain templates in four patients were reported as average DSC scores. Wilcoxon Signed Ranks Test at 95% confidence interval was applied to compare the accuracy of image registration scores of newly developed PET-DTI and the conventional PET-T1 templates using SPSS software.

Results

1. Image registration quality assessment in four dementia patients

The DSC score was calculated based on the lateral ventricle area in the whole brain images. The results showed that the DSC score of PET-DTI normal brain template was higher than PET-T1 normal brain template and it has a DSC value closest to 1 (Table 1 and 2).

2. Accuracy scores of image registration measurement by Nuclear Medicine Radiologists

The applications of PET-DTI and PET-T1 templates provided the perfect registration for the edge area. However, the application of PET-DTI template gave better registration for the inner edge area. The registration score was 2.89, compared to 2.31 for the conventional PET-T1W templates (Table 3). The averaged registration scores of the PET-DTI template were significantly higher than the PET-T1 template (p=0.001).

Table 1 DSC score of PET-DTI normal brain template registration with four patients.

Patient	Lateral ventricle area (pixel)		DSC Score
	PET-DTI template	PET brain image	
1	1081±20.76	1634±23.28	0.80
2	1046±16.38	1073±17.14	0.99
3	1031±17.63	1022±24.87	1.00
4	1180±21.16	1055±27.50	0.94

Table 2 The DSC score of PET-T1 normal brain template registration with four patients.

Patient	The lateral ventricle area (pixel)		DSC Score
	PET-DTI template	PET brain image	
1	788 ± 10.32	1824 ± 23.61	0.60
2	744 ± 9.77	945 ± 14.67	0.88
3	810 ± 9.07	998 ± 19.15	0.90
4	1031 ± 19.84	1207 ± 29.68	0.92

Table 3 The accuracy scores of images overlay between the developed method (PET-DTI template) and the standard method (PET-T1 template).

	Registration score			
	PET-DTI template		PET-T1 template	
	Outer edge [a]	Inner edge [a]	Outer edge [a]	Inner edge [a]
Radiologist No.1	3.00 ± 0.00	2.92 ± 0.17	3.00 ± 0.00	2.63 ± 0.14
Radiologist No.2	3.00 ± 0.00	2.75 ± 0.29	3.00 ± 0.00	1.81 ± 0.13
Radiologist No.3	3.00 ± 0.00	3.00 ± 0.13	3.00 ± 0.00	2.50 ± 0.20
Average score	3.00 ± 0.00	2.89 ± 0.19	3.00 ± 0.00	2.31 ± 0.16

[a] *Averaged across 4 reference areas.*

Discussion

This study demonstrated the feasibility of using PET-DTI brain template to cope with the miss-registration due to brain scans using DTI. The construction of PET-DTI based template was similar to the standard template derived from T1W images. When validated our proposed template in a small number of dementia patients, we found that the application of PET-DTI template improved the registration accuracy both qualitatively and quantitatively.

The structure and shape of the skull and cerebral cortex might be different among different ethnic groups.[20,21] The standard PET brain template was developed from Caucasian brains, so we constructed the PET-T1W brain template from Thai patients to reduce the bias on physiological differences among ethnics group. We followed the work of Chotipanich *et al*.[17] In that work, the normal PET brain template of Thai individuals for ^{11}C-PiB and ^{18}F-THK 5351 was constructed using statistical parametric mapping (SPM) software. It was found that the new PET brain template was better than the standard template in distinguish patients with dementia from those with normal brain conditions.

There was no difference in the registration quality observed at the outer edge of the cerebral cortex where the pathological deformation was rare in an early stage of dementia. Both MRI-T1 or MRI-DTI templates provided perfect registration. However, the registration quality at the inner edge of the cerebral cortex was significantly different between the two templates. The findings in this study indicated that the DTI registration provided more accurate results and could be applied to dementia patients with altered brain pathology. Since the brain atrophy let to an incomplete and less details in the MRI image, it increased a mismatch and reduced the quality of image registration between the PET image and the PET brain template. Moreover, a smaller reference point on the brain atrophy image resulted in the wrong referencing of radiopharmaceutical substance value on the standard template. Thus, using the MRI-DTI template with white matter track as a core reference could fix this problem. It improved the image registration quality and might provide more accurate radiopharmaceutical substance value referencing.

This study found that our method could improve the accuracy of spatial information (inner edge) of image registration between PET image and PET-DTI template evaluated by nuclear medicine radiologists, which corresponds to the previous study by Sungkarat et al.12 They reported that dog's probabilistic diffusion tensor imaging tractography map generated from DTI images could reduce overlapping problems and artifacts found around the edge of the cerebral cortex.

Additionally, the result from this current study corresponds to the study by Tritanon *et al*.[13] They reported that whole-brain probabilistic tractography normalization technique could improve interpretation of Alzheimer disease in human brain in particular around the edge of the cerebral cortex.

The limitation of our study is the small number of dementia patients. MRI scanning takes a long time and MRI-DTI is not a standard protocol, so only few patients completed all three imaging protocols (PET, MRI-T1W and MRI-DTI). However, the preliminary result of this pilot study indicated that the application of PET-DTI was more robust against brain atrophy than the conventional PET-T1W template. The template could be constructed for other PET radiopharmaceuticals.

Conclusion

This pilot study investigated the application of a new brain template for dementia diagnosis using DTI images. The experiment on four dementia patients revealed that PET-DTI based template yielded more accurate image registration than the standard PET-T1W brain template. Although intensive investigation is required for further studies, this current study had showed that the PET-DTI template had the potential to solve the limitation of the standard brain template in diagnosing dementia with brain atrophy using PET images.

Conflicting Interests

The authors declare that they have no conflicts of interest.

Ethics Approval

The study was granted ethics approval by the Human Research Ethics Committee of Chulabhorn Research Institute (Project code 050/2562).

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Patient radiation dose from fluoroscopic-guided transcatheter cardiac aortic valve implantation procedure: A single-center study in Thailand

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ABSTRACT

Background: The trend in the use of fluoroscopic-guided transcatheter aortic valve implantation (TAVI) is increasing because the procedure is less invasive than surgical procedure. However, high radiation doses have been reported with the procedure. Moreover, the amount of radiation received by patients undergoing TAVI has never before been registered in Thailand.

Objectives: This study aimed to investigate the radiation dose and the effects of sex and body mass index (BMI) on the radiation dose received by patients undergoing TAVI at Chulabhorn Hospital.

Materials and methods: Data were collected on the radiation dose received by patients undergoing the TAVI procedure during the first 26 months after the operation at the Cardiology Center, Chulabhorn Hospital. We recorded patient demographic data including age, sex, and BMI and the following measures of radiation dose from the procedure: the number of exposure images, air kerma-area product (P_{KA}), cumulative air kerma at the patient entrance reference point ($K_{a,r}$), and total fluoroscopy time.

Results: In total, 68 patients (35 male and 33 female) underwent TAVI, with median exposure images, P_{KA}, $K_{a,r}$, and total fluoroscopy time of 1,067 images, 166.14 Gy/cm^2, 1,171.50 mGy, and 31.90 minutes, respectively. The patient's sex did not affect total fluoroscopy time or the radiation dose received. Patients with BMI ≥30.0 kg/m^2 had the highest median values of P_{KA}, $K_{a,r}$, and total fluoroscopy time. Moreover, patients with BMI ≥18.5-24.9 kg/m^2 received higher doses of radiation than patients with BMI ≥25.0-29.9 kg/m^2; the result corresponded with longer total fluoroscopy time in the lower BMI category.

Conclusion: The amount of radiation that patients received during TAVI was appropriate for diagnosis and treatment. However, to ensure patient safety, operators should consider reducing the duration of radiation during the procedure. Data from this study are a starting point for the recording of radiation doses received by patients undergoing TAVI and can be used as a future dose reference.

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Introduction

Aortic stenosis is the most prevalent form of valvular heart disease worldwide and its prevalence continues to increase.[1] As a treatment approach for aortic stenosis, transcatheter aortic valve implantation (TAVI) plays an important role in patients at high risk for surgical aortic valve replacement.[2] Because this procedure is minimally invasive and allows patients to recover more quickly than with surgery, the number of patients receiving treatment with such procedures has increased.[3,4] In the TAVI procedure, X-ray fluoroscopy produces real-time radiographs that guide the catheter through blood vessels into the target treatment location in the heart, where ionizing radiation is used for a long period to create medical images, thus exposing patients to high doses of radiation. According to Koenig *et al.*, patients diagnosed and treated with X-ray fluoroscopy suffer from cutaneous radiation injury, which causes erythema within 2-24 hours of exposure to radiation doses higher than 2 Gy, a level within the range that causes skin abnormalities.[5,6] Generally, the dose rate for X-ray fluoroscopy in radiological interventions is in the range of 0.02-0.05 Gy/minute. In cardiac catheterization, the average radiation dose received by patients is 2.5 Gy and, in some cases, as high as 6.4 Gy-considerably above the threshold for skin abnormalities-potentially causing adverse events because of the deterministic effects of ionizing radiation.7 In addition, low-threshold radiation can induce biological changes in cells, leading to cancer with stochastic effects and side effects directly proportional to the amount of radiation received by the body. This is because ionizing radiation reacts with the patient's cells or tissues, causing cell death and abnormalities in cell function and various systems within the body.[8] Nonetheless, delivering the appropriate radiation dose for TAVI is necessary in the diagnosis and treatment of disease given the benefits of medical radiation to patients' quality of life. Therefore, establishing guidelines to monitor the dose of radiation received by patients undergoing TAVI is important.[9] The radiation dose received by the patient can be assessed using the air kerma-area product (P_{KA}), a parameter obtained by measuring the amount of radiation (Gy) released from the X-ray tube in area units (cm^2), the cumulative air-kerma value ($K_{a,r}$) at the patient entrance reference point, the dose at a defined reference point, and total fluoroscopy time.[10-12]

Information on the radiation dose from the procedure is important for determining whether the dose is suitable for the examination. The data are important for optimizing the patient's protection against medical exposure to radiation during cardiovascular catheterization. The diagnostic reference level (DRL) indicates the appropriate value of the radiation dose for the same type of radiological diagnosis from different sites at which the TAVI procedure is performed. Currently, DRL data for diagnostic and interventional radiology and cardiovascular catheterization in Thailand are being collected and compiled into a national DRL database through collaboration between the Department of Medical Sciences of the Thai Ministry of Public Health and hospitals across the country. However, given that TAVI is a new procedure that has only been implemented in Thailand in the past ten years by a small number of treating hospitals and for a limited number of patients, data on radiation doses during treatment with TAVI are insufficient.[13] Therefore, this study aimed to collect data on radiation doses received by patients undergoing TAVI at Chulabhorn Hospital, determine the median dose received from the procedure, and study the correlation between sex, body mass index (BMI), and radiation dose.

Materials and methods

Study design and sample selection

This study was approved by the Human Research Ethics Committee of Chulabhorn Research Institute (Project code 005/2563) as a retrospective and prospective study on patients undergoing TAVI fluoroscopy. The retrospective and prospective study was a preliminary investigation conducted at the Cardiology Center of the Chulabhorn Hospital between August 2019 and September 2021. The inclusion criterion was all patients who consented to undergo a TAVI procedure; the exclusion criterion was patients with incomplete radiation dose data in the data storage system.

Equipment performance and techniques

All procedures were performed in the same catheterization laboratory using a Philips Azurion 7 C20 with FlexMove (Philips Healthcare, Best, Netherlands) angiography system. A beam filtration control of 1 mm of aluminum with 0.1 mm copper filtration was used with fluoroscopy (7.5 frames per second) and cine-angiography (15 frames per second) X-ray imaging modes. The automatic control of X-ray exposure parameters was selected as the technical setting to ensure high image quality and a minimal dose for all patients undergoing the procedure. The radiation dose was registered using integrated dosimetry instrumentation. The equipment was subjected to annual quality assurance testing by the local medical physics services of the Department of Medical Sciences (Nonthaburi, Thailand).

Patients were consulted and treatments were planned before TAVI by a team of medical professionals in the TAVI conference committee. During the TAVI procedure, vascular access was gained by a multidisciplinary heart team using a percutaneous transfemoral approach and a physician who operated the fluoroscopy during the procedure, for a total of three operators. Clinical follow-up was performed 30 days after the procedure.

Data collection

The following data of patients undergoing TAVI procedures were recorded: demographics including age, sex, and BMI; dosimetry measurement (number of exposure images); air kerma-area product value (P_{KA}, in Gy/cm^2); cumulative air kerma at the patient entrance reference point ($K_{a,r}$, in Gy); and total fluoroscopy time (in min) obtained from the examination dose report in the structured radiation report, which is saved in the equipment upon process completion.[14]

Statistical analysis

Data were analyzed with descriptive statistics using the Stata/SE 12.1 (StataCorp, College Station, TX, USA) program and data were expressed as average, maximum, minimum, median, interquartile range, 1st quartile, and 3rd quartile values.

Results

Patient demographic data

Among the 68 patients undergoing TAVI in the department, 35 were male (51.47 %) and 33 were female (48.53 %), with a mean age of 80.25±5.51 years (range, 69-91 years) and mean BMI of 22.78±4.20 kg/m^2 (range, 14.34-37.50 kg/m^2). Overall, male and female patients had a similar mean age and BMI, as listed in Table 1.

Table 1 Patient demographic data.

Parameters	Mean±SD (range)
Age (years), N=68	80.25±5.51 (69-91)
BMI (kg/m2), N=68	22.7±4.20 (14.34-37.50)
Male, N=35 (51.47%)	
Age (years)	81.03±5.85 (69-91)
BMI (kg/m^2)	22.12±3.99 (14.53-37.50)
Female, N=33 (48.53%)	
Age (years)	79.42±5.00 (69-89)
BMI (kg/m^2)	23.48±4.03 (14.34-32.72)

Note: BMI: body mass index

Dosimetry measurement in patients undergoing TAVI

Table 2 Radiation dose received by patients undergoing transcatheter aortic valve implantation (TAVI).

Parameters (N=68, Female=33 and Male=35)	Dosimetry measurements			
	Number of exposure images	P_{KA} (Gy.cm^2)	$K_{a,r}$ (mGy)	Total fluoroscopy time (minutes)
Mean±SD	1,181.07±573.81	204.79±137.70	1,492.87±952.42	35.89±15.19
Median	1,067.00	166.14	1,171.50	31.90
1st Quartile (Q1)	789.75	113.50	874.50	26.58
3rd Quartile (Q3)	1,522.75	242.84	1,673.75	41.70
IQR	789.75-1,522.75	113.50-242.84	874.50-1,673.75	26.58-41.70

Note: IQR: interquartile range, P_{KA}: air kerma area product, $K_{a,r}$: cumulative air kerma at patient entrance reference point.

Table 3 Comparison of radiation dose received by patients undergoing TAVI between this study and international DRL.

National DRLs	P_{KA} (Gy.cm²)		$K_{a,r}$ (mGy)	
	Median	3rd Quartile (Q3)	Median	3rd Quartile (Q3)
Chulabhorn Hospital	166.14	242.84	1,171.50	1,673.75
Europe[11]	-	130.00	-	1,200.00
Finland[15]	-	90.00	-	-
Germany[15]	-	80.00	-	-
Australia[16]	47.86	78.38	721.00	1,124.00
Switzerland[17]	-	141.00	-	1,189.00
United States (US)[18]	188.00	321.00	1,639.00	2,420.00

DRLs, Diagnostic reference levels; P_{KA}, Air kerma area product; $K_{a,r}$, Cumulative air kerma at patient entrance reference point.

Table 4 Radiation dose for patients within genders.

Parameters	Male (N=35)	Female (N=33)
P_{KA} (Gy.cm²)		
Mean±SD	220.29±154.01	188.36±115.73
Median	166.84	162.56
1st Quartile (Q1)	128.62	109.15
3rd quartile (Q3)	237.66	246.87
IQR	128.62-237.66	109.15-246.87
$K_{a,r}$ (mGy)		
Mean±SD	1,644.09±1,046.00	1,332.48±811.66
Median	1,172.00	1,171.00
1st Quartile (Q1)	941.00	756.50
3rd quartile (Q3)	1,899.00	1,629.00
IQR	941.00-1,899.00	756.50-1,629.00
Total fluoroscopy time (minutes)		
Mean±SD	35.07±12.19	36.76±17.78
Median	32.40	30.70
1st Quartile (Q1)	26.50	26.40
3rd quartile (Q3)	42.60	41.40
IQR	26.50-42.60	26.40-41.40

IQR, Interquartile range; P_{KA}, Air kerma area product; $K_{a,r}$, Cumulative air kerma at patient entrance reference point.

Table 5 Radiation dose for patients according to different BMI categories.

	BMI categories (N=68)			
Parameters	**BMI <18.5 kg/m² (N=8, 11.76%)**	**BMI ≥18.5-24.9 kg/m² (N=42, 61.76%)**	**BMI ≥25.0-29.9 kg/m² (N=15, 22.06%)**	**BMI ≥30.0 kg/m² (N=3, 4.41%)**
P_{KA} (Gy.cm²)				
Mean±SD	134.81±51.67	197.19±118.04	212.39±157.48	459.81±156.31
Median	129.13	168.85	162.56	514.85
1st Quartile (Q1)	96.51	118.75	110.99	246.89
3rd quartile (Q3)	156.53	233.08	244.25	617.71
IQR	96.51-156.53	118.75-233.08	110.99-244.25	246.89-617.71

Table 5 Radiation dose for patients according to different BMI categories. (continued)

Parameters	BMI categories (N=68)			
	BMI <18.5 kg/m² (N=8, 11.76%)	BMI ≥18.5-24.9 kg/m² (N=42, 61.76%)	BMI ≥25.0-29.9 kg/m² (N=15, 22.06%)	BMI ≥30.0 kg/m² (N=3, 4.41%)
$K_{a,r}$ (mGy)				
Mean±SD	1,080.50±454.45	1,474.93±873.12	1,433.73±996.88	3,139.33±1087.44
Median	1,054.00	1,196.50	1,152.00	3,848.00
1st Quartile (Q1)	681.50	903.50	725.00	1603.00
3rd quartile (Q3)	1,289.50	1,669.25	1,899.00	3,967.00
IQR	681.50-1,289.50	903.50-1,669.25	725.00-1,899.00	1,603.00-3,967.00
Total fluoroscopy time (minutes)				
Mean±SD	31.69±11.63	35.50±15.76	35.55±11.17	54.33±19.39
Median	28.40	32.40	30.20	54.10
1st Quartile (Q1)	20.33	26.90	26.50	30.70
3rd quartile (Q3)	40.20	41.70	45.30	78.20
IQR	20.33-40.20	26.90-41.70	26.50-45.30	30.70-78.20

BMI, Body mass index; IQR, Interquartile range; P_{KA}, Air kerma area product; $K_{a,r}$, Cumulative air kerma at patient entrance reference point.

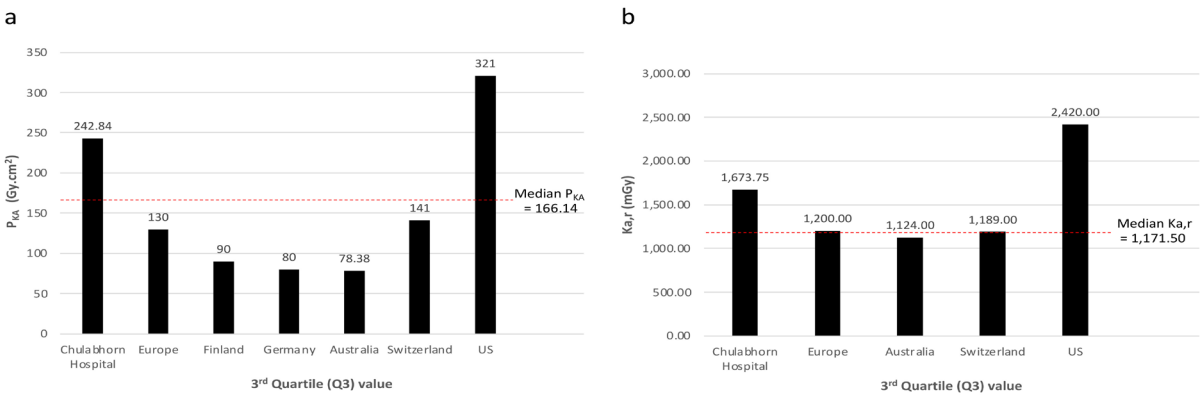

Figure 1 *Comparison of the third quartile (Q3) value of P_{KA} (a) and $K_{a,r}$ (b) undergoing TAVI between this study and international DRL. Dashed line: median value of this study, P_{KA}: air kerma area product, $K_{a,r}$: cumulative air kerma at patient, US: United States.*

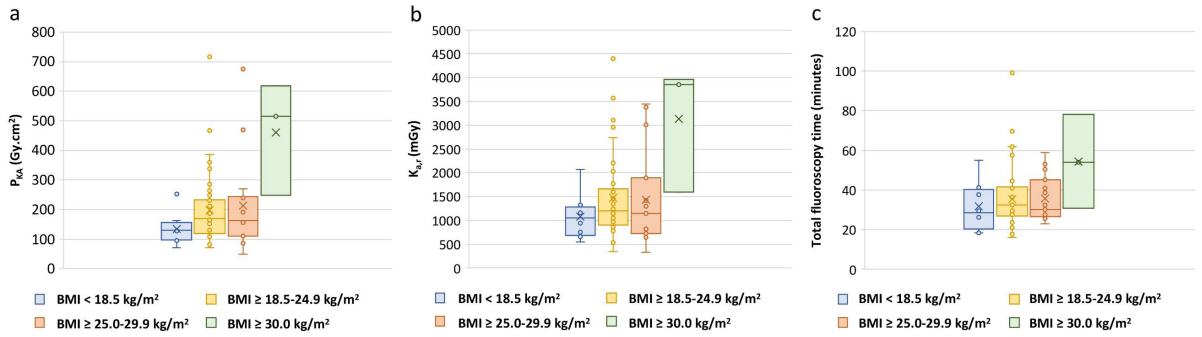

Figure 2 *Distribution of patient's radiation dose for TAVI procedure in the different BMI categories. The data are for P_{KA} (a), $K_{a,r}$ (b), and total fluoroscopy time (c). Box: the first and third quartiles, Line between box: median value.*

Discussion

This is the first Thai study of radiation doses in TAVI in which patient BMI and not patient sex affected the radiation dose received from the procedure. The number of patients undergoing radiological diagnosis increased in the US during the 2006-2016 period; the top four radiological diagnosis techniques included computed tomography, radiography and fluoroscopy, cardiac interventional fluoroscopy, and noncardiac interventional fluoroscopy.[19] Although cardiac interventional fluoroscopy is an important noninvasive procedure for the diagnosis and treatment of cardiovascular disease (with up to 1 million operations performed annually), TAVI is an important procedure in the treatment of aortic stenosis in high-risk patients who cannot undergo surgical procedures.[20] However, TAVI requires that X-ray fluoroscopy produce radiation that creates images during a prolonged and continuous process. Given that the process involves complicated procedures, the patient is exposed to high doses of radiation that may cause deterministic and stochastic side effects. The risk assessment of radiation exposure from X-ray fluoroscopic medical procedures is performed by measuring the values of cumulative air kerma at the patient entrance reference point ($K_{a,r}$)-which correlates with deterministic tissue effects such as skin erythema and epilation-and air kerma-area product (P_{KA}), which is used to estimate stochastic risks.[21, 22] This assessment is similar to the establishment of a DRL for cardiovascular catheterization.[12] The DRL values for cardiac interventional fluoroscopy were obtained by surveying radiation doses from similar X-ray fluoroscopy procedures in various departments. These values were used to compare the radiation dose received by patients from in-house X-ray machines to optimally protect patients against medical exposure to radiation. Guidance dose levels for diagnostic radiology were used in the US, Europe, and the United Kingdom until the current international recommendations for DRLs were established.[12,23] In addition, a US study of radiation doses received by patients undergoing cardiac interventional fluoroscopy between 2006 and 2016 found that the TAVI procedure was promising and the amount of radiation received by patients was reduced from the level originally observed during the 1960-2006 period.[19] Results may be attributable to the monitoring and evaluation of the patient's radiation doses in each instrument or in each standardized examination. As a result, several organizations worldwide are now aware of the importance of radiation dose assessment in patients and medical radiation users have become more knowledgeable in controlling, optimizing, and monitoring radiation doses. Moreover, technology has been developed and techniques have been modified to reduce the amount of radiation used in the TAVI procedure.

In this study, all patients undergoing TAVI were older adults and males and females were similarly represented. Correspondingly, the incidence of aortic stenosis among the population is considerably higher in older adults than in younger individuals and male and female patients are treated equally with TAVI.[1,24] Notably, the radiation doses received by patients as measured by median P_{KA}, $K_{a,r}$, and total fluoroscopy time were similar between males and females, indicating that sex does not affect the duration of the procedure or the radiation dose received from the procedure. However, previous studies report the effect of patient size or BMI on the radiation dose received by the patient. Patients who were obese or had a BMI higher than 30.0 kg/m^2 had higher radiation exposure from cardiac catheterization and statistically significant increases in P_{KA} and $K_{a,r}$ compared with patients with lower BMI values.[2,5] In this study, male and female participants had similar BMI values; therefore, the median values of P_{KA} and $K_{a,r}$ were similar. Notably, when patients were grouped according to BMI into four categories regardless of sex, patients with a BMI higher than 30.0 kg/m^2 received the highest radiation dose. As previously reported, higher BMI is associated with higher P_{KA} (dose area product) and $K_{a,r}$ values, likely because the potential and current of the X-ray machine tube are altered by higher BMI levels to maintain radiographic image quality, hence increasing the radiation dose received by patients.[23,25-27] Therefore, fluoroscopy procedures in larger patients may increase the risk of radiation exposure, which may result in deterministic and stochastic effects in patients. However, patients with the highest BMI values in this study were subjected to the longest total fluoroscopy time. This may be a limitation of a study with a small sample size because a correlation between increased BMI and the procedure's total fluoroscopy time has not been reported.[21] Furthermore, we observed that patients with BMI ≥18.5-24.9 kg/m^2 had higher P_{KA} and $K_{a,r}$ values than those with BMI ≥25.0-29.9 kg/m^2 because of longer total fluoroscopy time. Consequently, the duration of radiation during the procedure is an important element in determining the radiation dose received by patients. Therefore, in cases for which the duration of the procedure cannot be shortened, appropriate adjustments should be made to techniques, the rate of radiation use, and visualization modes.

The TAVI procedure involves a higher variety of radiation doses than other interventional cardiology procedures and reporting of the procedure in the national DRL database is still lacking in Thailand.[11,28] Additionally, this dataset is from only the first 2 years of the department's use of the procedure and a learning curve remains for the operator. The result of this study revealed that the radiation dose as measured by the relevant parameters -P_{KA}, $K_{a,r}$ and total fluoroscopy time -was different for each patient; this may be caused by factors such as operator technique and procedure complexity.[29] The study results provided a typical value or a median P_{KA} of 166.14 Gy/cm^2 whereas international DRLs of previous studies were in the range of 78.38-140 Gy/cm^2.[11, 15-17] The higher P_{KA} value in this study compared with the DRL of other countries could be attributed to procedure performance during femoral access (which widely opens the radiation field size and requires a longer time during the procedure), beginners' experience, the complexity of lesions in each case, and differences in patient anatomy that may have increased procedure duration.[18, 30-32] However, the other typical value-the median $K_{a,r}$ of 1,171.50 mGy was in the

range of 1,124-1,200 mGy of the international DRLs of previous studies.[11, 26-28] This value from our study is similar to DRLs of other countries. When comparing the radiation dose received by patients undergoing TAVI in a single-center study in a US hospital that used the same methods as in our study, the typical median values of P_{KA} and $K_{a,r}$ were approximately two times lower than US DRL values (P_{KA} and $K_{a,r}$ of 321 Gy/cm^2 and 2,420 mGy, respectively).[29] Admittedly, this could be attributable to the smaller body size of Thai patients, and therefore lower BMI and body surface area, and to different sets of image creation techniques or modes across various facilities. Overall, the median values of radiation dose received by TAVI patients in this study were below the threshold defined in the Society of Interventional Radiology guidelines for patient radiation dose management; these included P_{KA} (<500 Gy/cm^2), $K_{a,r}$ (<5,000 mGy), and total fluoroscopy time (<60 minutes).[18] However, in-house surveillance of the medical radiation dose is still a critically important concern.

The limitations of this study include its small sample size and data collection from a single piece of equipment in a single organization. However, the data from this study can be used to report radiation doses received by patients undergoing TAVI-a dataset that is currently underwhelming and insufficient. Furthermore, the median dose results of this study were compared with international DRLs, but do not account for different patient body habitus. Therefore, a national or Asian DRL database must be established in the future to allow the comparison of median dose values of radiation received by patients of similar body sizes undergoing TAVI. Furthermore, as recommended by the International Commission on Radiological Protection, continuous data collection and analysis must be performed to review DRL values every 3-5 years to determine the appropriate radiation doses for fluoroscopically guided TAVI procedures.

Conclusion

The amount of radiation that patients received from TAVI was appropriate for diagnosis and treatment. However, to ensure patient safety, operators should consider adjusting technique settings or reducing the duration of radiation during the procedure because patients in both the lowest and highest BMI categories in our study were subjected to long total fluoroscopy time leading to an increase in the radiation dose received. Data from this study are a starting point for recording radiation doses received by patients undergoing the TAVI procedure; data can be used as a future dose reference and compiled into a national DRL database.

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Conflicting interests

The authors declare that they have no conflicts of interest.

Ethics approval

This study was granted ethics approval by the Human Research Ethics Committee of Chulabhorn Research Institute (Project code 005/2563).

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Audit of computed tomography examinations from two selected radio-diagnostic centers in South-South Nigeria

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ABSTRACT

Background: Despite the fact that the number of CT exams is small among all radiography investigations, a high amount of medical radiation exposure comes from CT application. Most developed nations have adopted regular audits to ensure optimization of ionizing radiations in the CT examinations, but on the contrary, it has infrequently been performed in developing countries like Nigeria.

Objectives: This study was designed to carry out an audit of CT examinations at two selected diagnostic centers in the South-South region of Nigeria.

Materials and methods: This study was a retrospective cross-sectional study conducted in two radiological facilities, which involved 210 tomographs of the chest, head, and abdomen, selected using a convenient method. The CT examinations were done using the departmental protocols and the generated data were analyzed statistically using descriptive statistics.

Results: Head examination was the most commonly performed CT examination (56.7%), followed by abdominal 28.6 % and the least 14.8% was chest. The most common indication was a road traffic accident (RTA) 11.4%. The distribution of the type of CT machine that was used for the study showed that the Toshiba machine was used for most of the subjects 132 (62.9%) followed by Optima CT660 78 (37.1%). It was seen that 48.6% of the study used 0.75s, 40.5% used 0.5s, 10.5% used 0.35s and only 0.5% used 1s scan time. The effective doses were adult head (2.31±0.14), chest (4.65±0.21), abdominal (7.70±0.17), pediatric head (2.81±0.21), and pediatric chest (9.96±0.12).

Conclusion: The carrying out of clinical audits is imperative to ensure both safeties of patients and diagnostic accuracy.

Introduction

The introduction of computed tomography (CT) scanners into diagnostic Radiology was dated back to 1970s. CT has gained attractiveness globally owing to the substantial and life-saving clinical advantages.[1] However, the increase in the use of CT application has led to the emergence of radiologic concerns such as cancer risk because of the incremental effective dose (ED) associated with its use.[2] Despite the fact that numbers of CT is small among those radiography investigations, high amount of medical radiation exposure comes from CT application.[3]

It has been documented that approximately 1-14 mSv is the radiation dose associated with a typical CT scan, and this is equivalent to the annual dose received from natural sources of radiation, such as radon and cosmic radiation (1-10 mSv), depending on the location.[4] When organ specific cancer risk was adjusted for current levels of CT usage, it

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was estimated that 1.5-2% of cancer may eventually be caused by ionizing radiation used in CT.[5] This situation places an obligation on the community to review the amount of radiation set for CT scans and to improve the usefulness of the data for daily clinical practice.[6]

The ICRP recommended that medical activities involving ionizing radiation should fulfill the three basic principles of justification, optimization and dose limitation.[7-9] Therefore, proper clinical audit, practicing justification and development of optimized size specific scan protocols is important to keep the doses at an appropriate level and to reduce the risk associated with CT examination.[10] This involves taking into consideration the patient age, gender, technical parameters such as tube potential, time per rotation, detector configuration, beam collimation, pitch and effective mAs), CT Dose indicators (Volume CT Dose Index- CTDIvol and Dose Length Product-DLP), date of CT examination, sources of referrals for medical image, anatomical regions scanned, contrast agent used and route of administration.

Most developed nations has adopted regular audit to ensure optimization of ionizing radiations in the CT examinations, but on the contrary, it has infrequently been performed in developing countries like Nigeria.[11] This may have significant negative impact on the radiation doses received by patients undergoing CT investigations especially with the increasing numbers of CT scanners in our country. Hence, this study was designed to carry out an audit of CT examinations at two selected diagnostic centers in South-South region of Nigeria.

Materials and methods

This was a retrospective cross-sectional study conducted in two radiological facilities with functional CT scanners in Akwa-Ibom State and Rivers State, Nigeria. The study, which lasted for three months (May-July, 2019) involved 210 tomographs of chest, head and abdomen, selected using convenient method. Only tomographs obtained at least one month prior to this study and those with proper identification such as gender, age and date of examination were included in this study. Written permission for the collection of data was obtained from the study centers before accessing their CT archives.

The CT examinations were done using the departmental protocols, which included the scanogram and selection of specific options in operating console of the machine for the purpose of dose reduction, non-contrast axial slice at 2-5 mm thickness while slices were obtained following administration of low osmolar contrast medium (LOCM) at the dose of 300 mg/mL of the LOCM. Oral iodinated flavored contrast medium was administered for abdominal examinations, appropriate protocols was selected depending on the region of the body under examination. To further minimize the radiation dose of the patients, lead covers was applied to shield the body parts that were not under examination.

Effective dose is the only dose metric that can represent risk associated with CT examinations. A simplified method of estimating effective dose for CT examination entails multiplying the DLP value by an appropriate normalized specific k-coefficient (effective dose/DLP conversion factor). The k-coefficient is an effective dose conversion factor established by the National Radiological Protection Board (NRPB) for specific CT examinations, which take into account the patient's age and specific region being imaged.[12] The conversion factors have a wide age based range and do not take into account the patient's sex or specific scanner used and is the same for different scanners with the same parameters even though different scanners with different designs and beam filtration may produce different numbers for effective dose and DLP.[13]

The acquired images were transferred to the diagnostic workstation and were interpreted by at least one consultant radiologist. The information concerning the age, gender, and indication for CT examination were documented. The generated variables were collected using data capture sheet and analyzed statistically using descriptive statistics on SPSS version 21.

Results

Of the 210 tomographs, 113 (53.80%) were males and 97 (46.20%) females. Their age ranged from 1-78 years with a mean of 38.28±18.45 years. The grouped frequency table also showed that majority 33 (15.70%) were within the age of 35-39 years (Table 1). The most common indication for CT examination in the subjects was road traffic accident (RTA) 11.40%, followed by severe headache 9.00%, and multiple gunshot injuries (7.10%). other indications found in this study included severe cough, general body weakness, abdominal pains, abdominal swelling, jaundice, hypertensive heart disease, trauma etc. (Figure 1).

Table 1 Age group frequency distribution of the subjects.

Age groups	Frequency	Percent (%)
0-4	10	4.8
5-9	8	3.8
10-14	4	1.9
15-19	6	2.9
20-24	16	7.6
25-29	25	11.9
30-34	19	9.0
35-39	33	15.7
40-44	19	9.0
45-49	16	7.6
50-54	8	3.8
55-59	15	7.1
60-64	10	4.8
65-69	6	2.9
70-74	8	3.8
>75	7	3.3
Total	210	100.0
Gender		
Male	113	53.8
Female	97	46.2

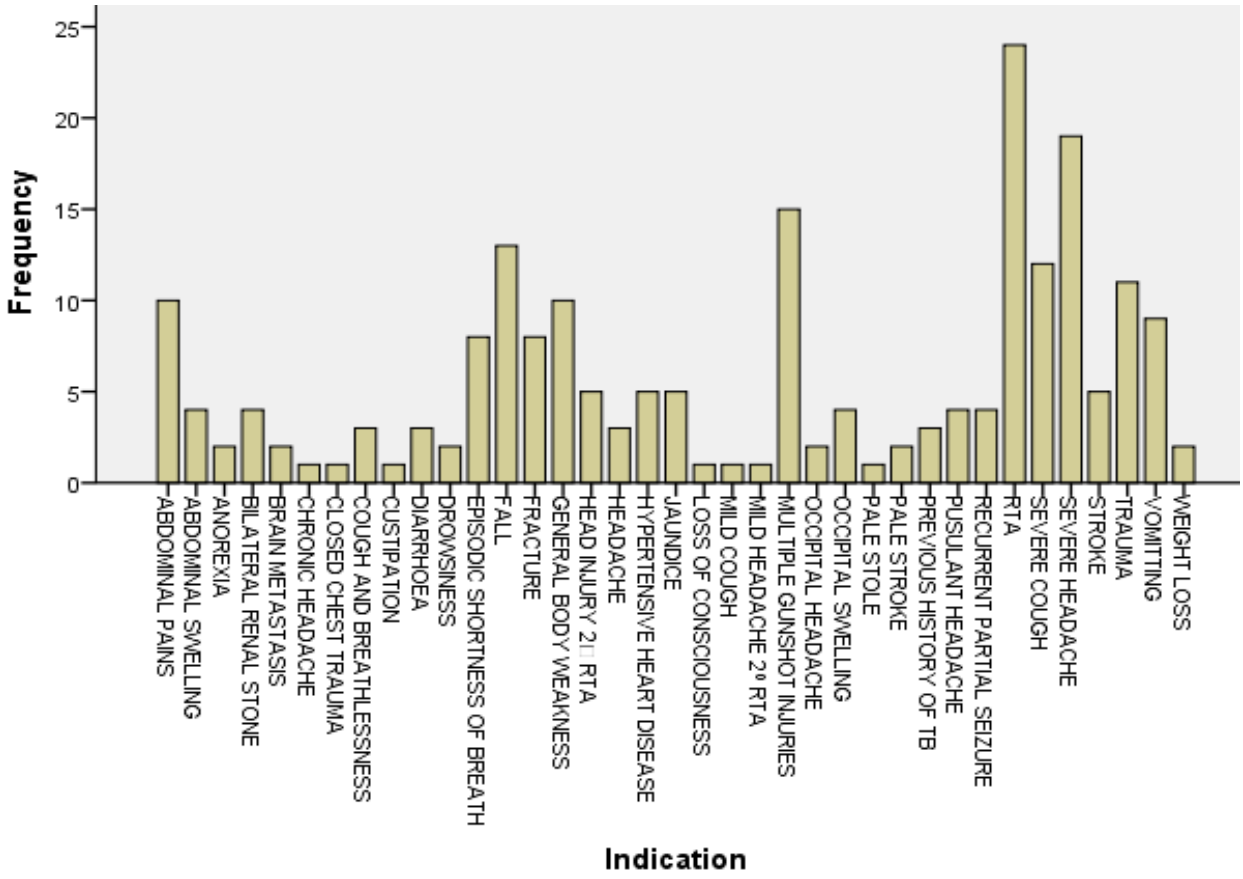

Figure 1. *Usual indications for CT scan performed on the subjects.*

Figure 2 shows the types of CT examination performed on the subjects. Head examination was most commonly performed in 56.70% followed by abdominal CT 28.60% and the least 14.80% was Chest CT examination. The distribution of the type of CT machine that was used for the study showed that Toshiba machine was used for most of the subjects (62.90%) followed by Optima CT660 (37.10%) (Table 2). It was seen that 48.60% of the study used 0.75s, 40.50% used 0.50s, 10.50% used 0.35s and only 0.50% used 1s scan time (Table 2).

Table 2 Cross tabulation of the scan time and machine used.

Time per rotation (sec)	CT machine		Total
	OPTIMA CT660	TOSHIBA	
0.35	11	11	22
0.50	25	60	85
0.75	42	60	102
1.00	0	1	1

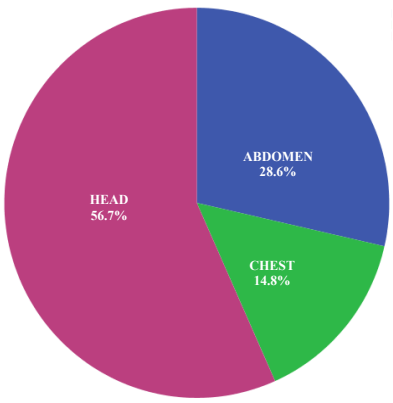

Figure 2. *Types of CT examination performed on the subjects.*

Table 3 shows comparison of adult head, chest, and abdominal CT dose values with Dose Reference Level (DRL) given in the international guidelines (14-15). Group 1 (16 years and above) was imaged according to the protocols set by the Optima and Toshiba. The technical factors and radiation doses at routine adult heads, chest and abdominal is reported in table 4. Table 5 shows comparison of pediatric head, chest, and abdominal CT dose values with DRLs given in the international guidelines Group 2 (0-15 years) was imaged according to the protocols set by the Optima and Toshiba. The effective doses were adult head (2.31±0.14), chest (4.65±0.21), abdominal (7.70±0.17), pediatric head (2.81±0.21) and pediatric chest (9.96±0.12) (Table 6).

Table 3 Comparison of head, chest, and abdominal CT dose values with DRLs given in the international guidelines.

Examination	Dose parameter	Group 1	EU (2004)	IAEA (2006)
Adult head CT	CTDIvol (mGy)	53.19	60	47
	DLP (mGy.cm)	1098.6	1050	1050
Adult chest CT	CTDIvol (mGy)	7.903	30	9.5
	DLP (mGy.cm)	332.1	650	447
Adult abdominal CT	CTDIvol (mGy)	10.9	35	10.9
	DLP (mGy.cm)	513.2	780	696

Table 4 Important technical factors at routine adult heads, chest and abdominal CT examinations in the center.

Examination	Parameters	No of patients
Adult head CT		100
	Average age	43.23
	mA	127-410
	Rotation time	0.7
Adult chest CT		30
	Average age	18.0
	mA	150-480
	Rotation time	0.43
Adult abdomen CT		57
	Average age	39.98
	mA	80-480
	Rotation time	0.5

Table 5 Comparison of pediatric head, chest, and abdominal CT dose values with DRLs given in the international guidelines Group 2 (0-16 years) was imaged according to the protocols set by the Optima and Toshiba.

Examination	Parameters	Group 2	IAEA (2004)	DDM2 (2012)
Pediatric head CT	Number of patients	18		
	Average age	5.4		
	Ma	151-450		
	CTDIvol	38.3		
	DLP	669.3	600	470
	Rotation time	0.6	0.5	0.5
Pediatric chest CT	Number of patients	2		
	Average age	9		
	mA	119		
	CTDIvol	7.0		
	DLP	765.8	430	450
	Rotation time	0.35	0.5	0.5
Pediatric abdomen CT	Number of patients	3		
	Average age	10		
	mA	70-119		
	CTDIvol	3.7		
	DLP	352.3	450	475
	Rotation time	0.43	0.5	0.5

Table 6 Effective dose for adult and pediatric head, chest and abdominal CT examination.

Examination	Effective Dose (mSv)
Adult head CT	2.31±0.14
Adult chest CT	4.65±0.21
Adult abdominal CT	7.70±0.17
Pediatric head CT	2.81±0.23
Pediatric chest CT	9.96±0.12
Pediatric abdominal CT	5.28±0.22

Discussion

The purpose of this study was to perform an audit of CT examinations in diagnostic centers in South-South region of Nigeria. This was done according to the recommendations and guidelines of radiation protection report No.159, which describes how to implement a structured audit in a Radiology Department in compliance with the most recent guidelines from International Atomic Energy Agency (IAEA) (16). A total of 210 subjects including 113 males (53.8%) and 97 females (46.2%) with age ranged from 1 year to 78 years old were included in the study. Three types of examination were evaluated namely, routine head/brain CT, abdominal CT and chest CT. For each patient, demographic information (age, sex), exposure parameters like tube potential (kVp), mA, time per rotation, and dose parameters (CTDIvol and DLP) were recorded. Data was obtained from two diagnostic centers in Port Harcourt and Uyo metropolises in Nigeria.

Toshiba machine was used in 132 (62.9%) of the subjects and Optima CT660 78 (37.1%) with rotation time ranging from (0.35-1.00 sec). The DRL for the anatomical regions, head, chest and abdomen for both female and male patients were obtained. Two groups were considered (Group 1 and Group 2). Group 1 consisted of adult patients (17 year and above) who were imaged according to the protocols set by the Optima and Toshiba and Group 2 consisted of pediatrics (0-16 years) who were images according to the protocols set by Optima and Toshiba. Table 3 showed the comparison of adult head, chest and abdominal CT dose values (CTDIvol and DLP) with DRLs given in the international standard.[14-15] It was seen that the radiation for Group 1 were lower than the international guidelines. This indicates that radiation dose is kept within limits and guidelines.

The mean weighted CT dose Index CTDIvol for adult head Group 1 was (53.10 mGy) for head CT in the entire sample (female and male patients was comparable to values reported by.[19,20] The mean DLP (1098.60 mGy.cm) for head CT was higher than that of the other authors such as 740 mGy.cm,[21] 587 mGy.cm,[22] 787 mGy.cm.[23] Also, the mean weighted CT dose index for adult abdominal CT (Group 1) was 10.9 mGy, which is in the range of values (10-29 mGy) reported by.[19,24,25] The mean DLP for abdominal CT (513.2 mGy.cm) was lower than the values reported by (25) (493-551 mGy.cm). Moreover, the mean weighted CT dose index (7.9 mGy) for chest CT was lower than the value reported in the previous IAEA coordinated research project (16.20 mGy).[23] The mean DLP (33.20 mGy.cm) for chest CT was lower than the IAEA reported value 455 mGy.cm.[26]

Table 5 showed the comparison of pediatric head and chest dose values (CTDIvol and DLP) with DRLs given in the international standard.[14,16,18] It was seen that the CTDIvol for group 2 were much lower than the international guidelines and the DLP were much higher than that of the international guidelines. The mean weight CT dose index CTDIvol for pediatric head was (38.3mGy.cm) for age 5 yrs. This variation may be as a consequence of differences in CT scanner design and examination protocols.[12]

The mean DLP value of 669.3 mGy.cm for pediatric head CT was higher than the ones reported by IAEA (600 mGy.cm)[15] and Dose Datamed 2 Project- DDM2 (47 0 mGy.cm).[18] Also the mean CTDIvol for pediatric chest CT was (7.00 mGy.cm) which was in range of values reported by Klang *et al*.[2] The mean DLP for pediatric chest CT (765.80 mGy.cm) was higher than 368 mGy.cm reported by DDM2.[18] However, the mean DLP for pediatric Abdominal CT (age 10) of 352.30 mGy.cm was lower than the values reported by IAEA, which was 450 mGy.cm. These differences in our findings could be attributed to scanners having varying number of detector rows and different brand have specific manufacturer detector configuration and dose compensation mechanism that respond to exposure contrarily from each other and thus produce dissimilar doses.[12]

It was seen that the effective dose for adult head CT examination was 2.31 mSv, adult chest CT was 4.65 mSv, and adult abdomen CT was 7.70 mSv. Also, the effective dose for pediatric head, chest and abdomen CT were 2.81 mSv, 9.96 mSv and 5.28 mSv respectively. According to Ploussi and Efstathopoulos a typical head CT scan which is the most frequent CT examination in adults and children delivers an effective dose of about 4 mSv.[28] Whereas the effective doses for the abdomen and coronary angiography CT examinations can reach 25 mSv and 32 mSv, respectively. Thus, as far as radiation risk effects are concern, radiation exposure from the studied CT examinations were far below the threshold.

Conclusion

Carrying out of clinical audits is imperative to ensure both safety of patients and diagnostic accuracy. Comparing the Local DRLs and the calculated effective doses with that of the international standards produced comparable safe results though with variations, which may be attributed to differences in CT scanner design and examination protocols.

Conflict interest

None declared among the authors.

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Determination of volume-specific correction factors and geometry effects of ^{90}Y activity measurement in dose calibrators

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ABSTRACT

Background: Yttrium-90 (^{90}Y) is widely used in nuclear medicine for therapeutic purposes. The radiation dose of radiopharmaceuticals relates to the activity of the radionuclide which is measured in the dose calibrator during radiopharmaceutical preparations.

Objectives: The objectives of this study were to determine volume-specific correction factors and investigate the geometry effects of ^{90}Y activity measurement in dose calibrators.

Materials and methods: Four dose calibrators from two institutes were independently measured. The 3-mL plastic syringe and the 10-mL glass vial were used to investigate the geometry effects using the initial calibration factors for each dose calibrator. The comparison between actual activity and measured activity was expressed as the percentage errors. For volume-specific correction factor, the value for each volume was calculated based on the actual and measured activity at 0.5, 1.0, 1.5, 2.0 and 2.5 mL.

Results: Percentage error showed that ^{90}Y activity measured in the 3-mL plastic syringe and the 10-mL glass vial were inaccurate. The activity measurements in the 3-mL plastic syringe were more accurate than in the 10-mL glass vial at all volumes for both containers in all dose calibrators. Our findings showed that increasing the volume of ^{90}Y could result in underestimate of the measured activity. The maximum volume dependence in the 10-mL glass vial was about 20%. Hence, the volume-specific correction factors were determined for the 3-mL plastic syringe and the 10-mL glass vial for all dose calibrators.

Conclusion: The geometry effect could impact the ^{90}Y activity measurement on the dose calibrators. Using the volume-specific correction factor for each geometry of ^{90}Y to compensate for the geometry effect could improve the accuracy of ^{90}Y activity measurement. However, the volume-specific correction factors are depended on the dose calibrators. Therefore, the institutes need to establish their own volume-specific correction factors for ^{90}Y activity measurement.

Introduction

Yttrium-90 (^{90}Y) is a pure high-energy beta emitting with maximum energy of 2.27 MeV and average energy of 0.9336 MeV that has recently been used in nuclear medicine as a therapeutic radiopharmaceutical in many diseases, for example, hepatocellular carcinoma, non-Hodgkin's lymphoma and rheumatoid arthritis.[1] The radioactivity

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measurement of radiopharmaceuticals administrated to the patients should be considered due to it could influent the efficacy of the treatment. In nuclear medicine practice, the standard instrument used to measure the activity of radiopharmaceuticals is a radionuclide activity calibrator (or also called "a dose calibrator").

Dose calibrator is a gas-filled detector operated in the ionization chamber region that contains the isotope selector and calibration factor (or "dial setting") for the activity measurement of each radionuclide. In general, the calibration factor of each dose calibrator is recommended by the manufacturer which is specific to the geometry of the radionuclide. According to international recommendations, the error of administered activity for therapeutic radiopharmaceutical must not exceed 10% of the prescribed dose.[2] For ^{90}Y activity measurement, the containers with different compositions, thicknesses and source geometries can impact the accuracy ^{90}Y activity measurement due to the bremsstrahlung radiation produced from the ^{90}Y radionuclide with container and the dose calibrator chamber wall. Additionally, several studies showed that the calibration factor of ^{90}Y provided by the manufacturer of the dose calibrator might not be suitable for all the conditions of ^{90}Y activity measurement. [2-7]

Therefore, the primary objective of this study was to investigate the accuracy of ^{90}Y activity measurement in dose calibrators by varying the containers and the volumes of ^{90}Y using the initial calibration factor recommended by the manufacturer and routine calibration factor for each dose calibrator. Besides, this study was also aimed to determine the volume-specific correction factors and investigate the geometry effects of ^{90}Y activity measurement in the dose calibrators.

Materials and Methods

Yttrium chloride ($^{90}YCl_3$)

$^{90}YCl_3$ solution was obtained from the National Centre for Nuclear Research, Radioisotope Centre (Polatom, Otwock-Swierk, Poland) with the activity of 10 mCi or 370 MBq. The product data sheet that indicated the traceable activity concentration, volume, and total activity of the $^{90}YCl_3$ was received. Hydrochloric acid (HCl) was used to adjust the volume of $^{90}YCl_3$ in two containers starting at 0.5 mL. Then, increase the volume of the $^{90}YCl_3$ by adding HCl to 1.0, 1.5, 2.0 and 2.5 mL respectively to investigate the geometry effect on the ^{90}Y activity measurement. The decay correction was applied for the calculation of the actual activity as follow equation:

$$A = A_0 e^{-\lambda t} \qquad (1)$$

Where A is the actual activity of $^{90}YCl_3$ at the time of measurement, A_0 is the initial activity of $^{90}YCl_3$ at the calibration time and $e^{-\lambda t}$ is the decay factor of $^{90}YCl_3$.

Dose calibrators

Four dose calibrators from 2 different centers were used in this work including 2 dose calibrators at the Division of Nuclear Medicine, Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine Ramathibodi Hospital and 2 dose calibrators at the Thailand Institute of Nuclear Technology (TINT).

At Faculty of Medicine Ramathibodi Hospital, the activity of $^{90}YCl_3$ was measured in ATOMLAB 100Plus dose calibrator (Biodex Medical Systems, USA) and CRC®-25 PET dose calibrator (Capintec Inc., USA). According to manufacturer's recommendation, the calibration factors for ^{90}Y measurement of Atomlab 100Plus and CRC®-25 PET dose calibrator were 375 and 074×10 respectively. At TINT, the activity of $^{90}YCl_3$ was measured in the CRC®-Ultra dose calibrator (Capintec Inc., USA) using the calibration factor of 048×10 and the Victoreen dose calibrator model 34-056 (Victoreen Inc.) using the calibration factor of 112.5×10.

Disposable syringe 3-mL with Combi-Stopper

For syringe measurement, 3 mCi of $^{90}YCl_3$ was aliquot into the 3-mL plastic syringe (Terumo, Japan) before adding HCl to the total volume of 0.5 mL and closed the end of the syringe with the Combi-Stopper (Braun, Melsungen, Germany). To measure the activity, the background radiation was measured and subtracted before measuring at least 3 times to obtain the average of measured activity in dose calibrators. The measurements were repeated by increasing the volume of $^{90}YCl_3$ to 1.0, 1.5, 2.0 and 2.5 mL respectively.

Glass vial 10-mL with rubber stopper

For vial measurement, 3 mCi of $^{90}YCl_3$ was aliquot into the 10-mL glass vial (Farris Laboratories Inc, Tx, USA) before adding HCL to the volume of 0.5 mL and closed the end of the vial with a rubber stopper. To measure the activity of $^{90}YCl_3$, the background radiation was measured and subtracted before measuring at least 3 times to obtain the average of measured activity in dose calibrators. The measurements were repeated by increasing the volume of $^{90}YCl_3$ to 1.0, 1.5, 2.0 and 2.5 mL respectively.

Investigation of the geometry effect

The actual activity and averaged measured activity for each geometry were compared to investigate the geometry effect of $^{90}YCl_3$ activity measurement in the term of percentage error that was calculated as follows:

$$\text{Percentage error (\%)} = \frac{\text{(Averaged measured activity-Actual activity)}}{\text{Actual activity}} \times 100 \qquad (2)$$

Determination of volume-specific correction factors for dose calibrators

Volume-specific correction factor for each geometry of $^{90}YCl_3$ was calculated as follows:

$$\text{Volum specific correction factor} = \frac{\text{Actual activity}}{\text{Average measured activity}} \qquad (3)$$

Results and Discussion

The response of dose calibrators to $^{90}YCl_3$ activity reading in different containers with the initial calibration factor recommended by the manufacturer and the influence of filling volume were explored in this work. The supplier's traceable activity concentration was used

as a reference activity, the decay corrected activity was calculated at the time of measurement.

The percentage errors between the measured activity and the actual activity in different dose calibrators with the initial calibration factors; ATOMLAB 100Plus, CRC®-25 PET, CRC®-Ultra and VICTOREEN model 34-056 are plotted in Figure 1 to Figure 4 respectively.

According to our findings with the initial calibration factors in four dose calibrators, almost all the percentage errors of the 3-mL plastic syringe were less than the 10-mL glass vial from four dose calibrators. Although one notice with volume of 0.5 mL measured on the VICTOREEN dose calibrator, the 10-mL glass vial was more accurate.

For the ATOMLAB 100 Plus dose calibrator with the initial calibration factor of 375, the percentage error of less than 5% were founded in the $^{90}YCl_3$ in the 3-mL plastic syringe in all volumes. Whereas the percentage errors were increased with the volume of $^{90}YCl_3$, the percentage errors were ranged between 17.98 to 24.65% in the 10-mL glass vial. According to manufacturer recommendation, the initial calibration factor of 375 of the ATOMLAB 100Plus dose calibrator was calibrated for the ^{90}Y-Zevalin with a volume of 3-9 mL in the 10-mL plastic syringe. In the 3-mL plastic syringe, our result showed that the percentage error for volume of 1 mL was higher when compared with the volume of 1.5, 2 and 2.5 mL. Hence, this correlated with our findings that the measurements in the plastic syringe were more accurate than the glass vial at all volumes, additionally for the plastic syringe, the higher volumes were resulted more accurate than the small volume.

Similar results were shown in the CRC®-25 PET and the CRC®-Ultra dose calibrators. The accuracy of measurement was better in the 3-mL plastic syringe when compared with the 10-mL glass vial. The differences of activity between the actual activity and the measured

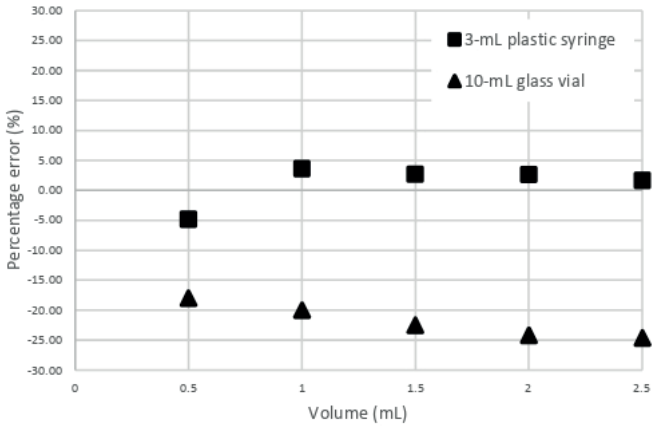

Figure 1 *Percentage errors between the measured activity and the actual activity measured on the ATOMLAB 100Plus dose calibrator with the initial calibration factor of 375.*

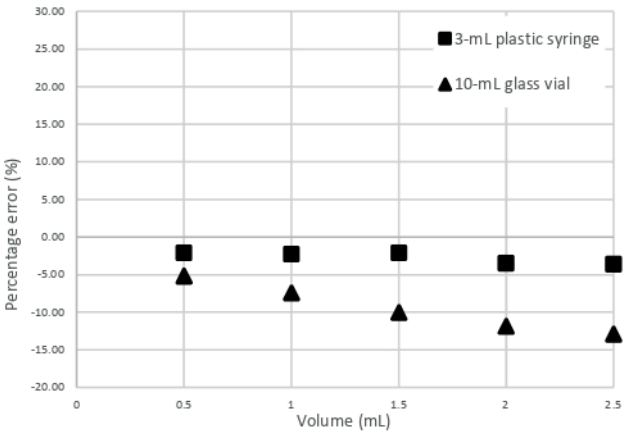

Figure 2 *Percentage errors between the measured activity and the actual activity measured on the CRC®-25 PET dose calibrator with the initial calibration factor of 074×10.*

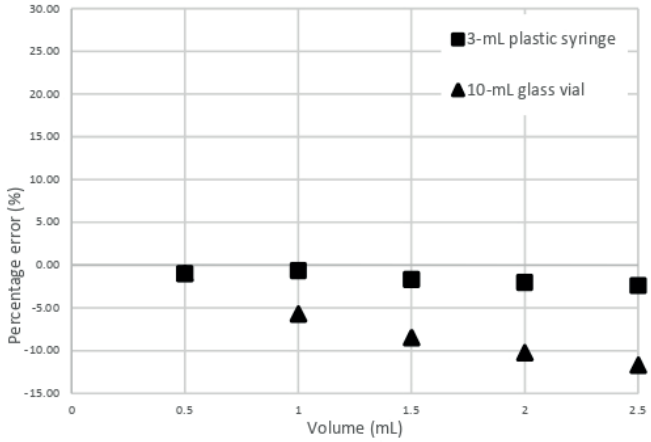

Figure 3 *Percentage errors between the measured activity and the actual activity measured on the CRC®-Ultra dose calibrator with the initial calibration factor of 048×10.*

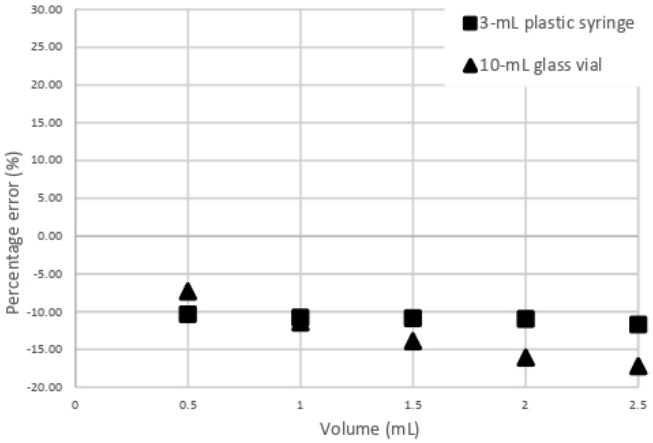

Figure 4 *Percentage errors between the measured activity and the actual activity measured on the VICTOREEN dose calibrator with the initial calibration factor of 112.5×10.*

activity were increased with the volume. Differences of up to 12.91 and 11.72 % for 2.5 mL of $^{90}YCl_3$ in the 10-mL glass vial for the CRC®-25 PET and the CRC®-Ultra dose calibrators respectively. For the CRC®-25 PET dose calibrator, the calibration factor of 074×10 is the routine calibration factor that was calibrated for ^{90}Y-citrate colloid measurement in the plastic syringe by user. As stated by Capintec™ manufacturer, the calibration factor of 48x10 (for the CRC®-Ultra dose calibrator) was calibrated for the 5 mL ^{90}Y solution in the 0.6 mm. glass ampoule.

In case of the VICTOREEN dose calibrator, almost all $^{90}YCl_3$ measurements with the routine calibration factor for ^{90}Y of 112.5x10 were differed from the actual activity more than 5% at all volumes. Differences of up to 11.76 and 17.24% were also found for the 2.5 mL $^{90}YCl_3$ solution in the 3-mL plastic syringe and the 10-mL glass vial respectively. This may occur from two reasons, firstly, the routine calibration factor for ^{90}Y of 112.5x10 is not suitable for the measurement in the 3-mL plastic syringe and the 10-mL glass vial because we don't know that the routine calibration factor for ^{90}Y of 112.5x10 was calibrated in which geometry of ^{90}Y. Secondly, the VICTOREEN dose calibrator was used for long time ago, the leakage of gas that filled in the chamber may cause of the error in the measurement.

The volume-specific correction factors for the plastic syringe and glass vial were also derived for ATOMLAB 100Plus, CRC®-25 PET, CRC®-Ultra and VICTOREEN model 34-056 dose calibrators (as tabulated in Table 1 to Table 4 respectively).

Table 1 Volume-specific correction factors for each volume of $^{90}YCl_3$ in both containers for the ATOMLAB 100Plus dose calibrator.

Volume (mL)	For 3-mL plastic syringe	For 10-mL glass vial
0.5	1.0490	1.2195
1.0	0.9675	1.2521
1.5	0.9737	1.2913
2.0	0.9735	1.3170
2.5	0.9832	1.3303

Table 2 Volume-specific correction factors for each volume of $^{90}YCl_3$ in both containers for the CRC®-25 PET dose calibrator.

Volume (mL)	For 3-mL plastic syringe	For 10-mL glass vial
0.5	1.0240	1.0528
1.0	1.0241	1.0833
1.5	1.0208	1.1128
2.0	1.0387	1.1346
2.5	1.0356	1.1451

Table 3 Volume-specific correction factors for each volume of $^{90}YCl_3$ in both containers for the CRC®-Ultra dose calibrator.

Volume (mL)	For 3-mL plastic syringe	For 10-mL glass vial
0.5	1.0102	1.0101
1.0	1.0068	1.0607
1.5	1.0173	1.0929
2.0	1.0210	1.1145
2.5	1.0247	1.1328

Table 4 Volume-specific correction factors for each volume of $^{90}YCl_3$ in both containers for the VICTOREEN model 34-056 dose calibrator.

Volume (mL)	For 3-mL plastic syringe	For 10-mL glass vial
0.5	1.1161	1.0794
1.0	1.1212	1.1293
1.5	1.1226	1.1621
2.0	1.1236	1.1918
2.5	1.1333	1.2083

Based on our study, inaccurate measurement may lead to error in administration of radiopharmaceutical. For clinical nuclear medicine, the administration of radiopharmaceutical should not be differed by more than ±10% of prescribed dose. For our results, the error in ^{90}Y measurement results from the interaction of radionuclide and surrounding materials which can produce bremsstrahlung radiation. The amount of bremsstrahlung radiation is proportional to the atomic number of materials that interact with a beta particle. In our work, the atomic number of the plastic syringe is lower than the glass vial, we assumed that the beta particles can travel through the plastic and interact with the structure of the dose calibrator which can generate more bremsstrahlung radiation so the measured activities of $^{90}YCl_3$ in the 3-mL plastic syringe were higher than in the 10-mL glass vial.[8, 9]

According to the reports from several studies, the uncertainty of the dose calibrator can occur when variations of the radiation sources geometry including type, size, thickness and shape of container and also volume of source.[5, 10-13] D Tyler and MJ Woods revealed the geometry effect of low energy photon activity measurement in the NPL (National Physical Laboratory) of the UK (United Kingdom) Report 56. Their results indicated that variations of the dose calibrator responses were certainly observed when the size of the container and volume of the source were varied especially for a beta emitter radionuclide like ^{90}Y.[5] In addition, Karsten *et al*. also reported the effect of ^{90}Y containers on 21 dose calibrators in 19 hospitals in Germany. Up to 95% of measurement

with the P6-type vials were deviated within ±10% from th reference activity. However, the deviation was larger whe remeasured the ^{90}Y activity in their own syringe geometry. [12]

In our work, our resulted indicated that the one calibration factor was not suitable for measurement in al volumes. Consequently, the volume-specific correctio factors could use to improve the accuracy of $^{90}YCl_3$ activity measurement. As seen in our study, the differenc between measured and actual activity can be as much a 30%. This was agreed as the findings by many studies. [11, 13, 14] Hence, the volume-specific correction factors should be determined and applied to compensate the volume effect for ^{90}Y measurement.

Conclusion

This study demonstrated that the accuracy of dose reading of ^{90}Y was very sensitive by the geometry with the differences in containers and the volumes. The initial calibration factor could lead up to 25% error when measuring with the difference container and volume as specified by the dose calibrator's manufacturer. Therefore, it is recommended that the condition of initial calibration factor for each dose calibrator should be checked prior to the dose measurement, especially for ^{90}Y which the dose measurement is primarily affected from bremsstrahlung radiation produced from high energy beta interactions.

Based on our resulted, the effect of changing the volume could impact the accuracy as well even with the correct container. Using the volume-specific correction factor could improve the accuracy of ^{90}Y activity measurement. Hence, the institutes need to establish their own volume-specific correction factors for ^{90}Y activity measurement based on the stated pre-calibrated activity from manufacturer.

Conflict of interest

The authors declare no conflict of interest.

Ethic approval

This research is not involving with human subjects.

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Role of computed tomographic enterography for evaluation of small bowel diseases: A cross-sectional study

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ABSTRACT

Background: Computed tomographic enterography (CTE) is a newer non-invasive modality having distinct advantages over conventional CT and capsule endoscopy.

Objectives: This technique allows faster evaluation of small bowel diseases in the endoscopically inaccessible segments. Being an operator-independent procedure, CTE is widely available and allows a better depiction of extra enteric complications. The aim is to evaluate CTE features of various small bowel diseases and the role of 2% mannitol for adequate small bowel distension.

Materials and methods: A cross-sectional study comprising 105 patients had presented with small bowel diseases. Patients in the age group of 10 to 85 years with complaints of fever, abdominal pain, nausea, vomiting, altered bowel habits, loss of appetite and loss of weight were included in this study. CTE images were analyzed to compare the diagnosis with the available histopathological and ultrasonography results.

Results: Among the study population, the majority had presented CTE features such as symmetrical wall thickening (53.3%), peri-bowel inflammatory changes (61%), mucosal hyperenhancement (39%), and mural stratification, i.e., target sign (33.3%). The majority of diagnoses of CTE were ileocecal tuberculosis (11.5%), small bowel inflammation (7.6%), and Crohn's disease (6.7%). Other conditions such as small bowel neoplastic masses, diverticula, ischemic bowel disease, bowel strictures, intussusception, and ulcerative colitis.

Conclusion: CTE has the vital role of first-line modality in the work-up of suspected small intestinal diseases and helps evaluate disease activity before endoscopy, particularly in inaccessible segments. It allows a better depiction of extra enteric complications of the bowel.

Introduction

Small bowel segment of the alimentary tube is the most challenging part of being examined due to its length, caliber, and overlapping loops.[1] Due to the caliber and size, the small intestinal loops are always under-evaluated both by conventional radiography and endoscopic modalities. Computed tomography (CT) has significantly evaluated extra-enteric manifestations of small bowel disease. In contrast, it is restricted to depicting luminal and bowel wall pathologies.[2] CT enterography (CTE), a new robust technique for characterizing small bowel disease, uses the current advanced technology of multidetector-row CT (MDCT). This technology is used in CTE and provides

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detailed evaluation and interpretation of mural and luminal features of the gut. An accurate depiction of peri-enteric tissues improves the assessment of disease complications and extends.[2,3] The modality allows better three-dimensional reconstructions (volume rendering, surface shading and multi-planar reconstruction display) and volume rendering through navigation (virtual CT endoscopy).[4] New scanners with the above technology help the isotropic acquisition of images during a single breath-hold and allow a high-resolution analysis of bowel features in a multiphasic manner.[2,5]

CTE differs from conventional abdominopelvic CT by using thin collimated slices and a high volume of contrast agent to display the small bowel wall and lumen effectively (Figure 1). This technique uses a neutral contrast material like water and an intravenous contrast agent to evaluate small bowel features such as hyper vascular lesions and hyper-enhancing segments, compared to the traditional follow-through examination.[6] Water is widely used as a neutral contrast material and has an excellent effect on the upper portion of the GIT. However, its use for distal small bowel is limited in clinical practice for the rapid absorption property.[7,8] An additive can cause slow water absorption by raising the solution's osmolarity.[1] *Mannitol* is one such additive, which is an inexpensive neutral oral contrast agent and easy to use. Due to iso-osmotic property, *mannitol* helps adequate small bowel distention making CTE an effective modality for evaluation of small bowel diseases.[9]

Our objective is to analyze CTE's role in detecting and characterizing small bowel pathologies by using mannitol for optimal bowel distension, thus making it more accessible in decision-making for further management.

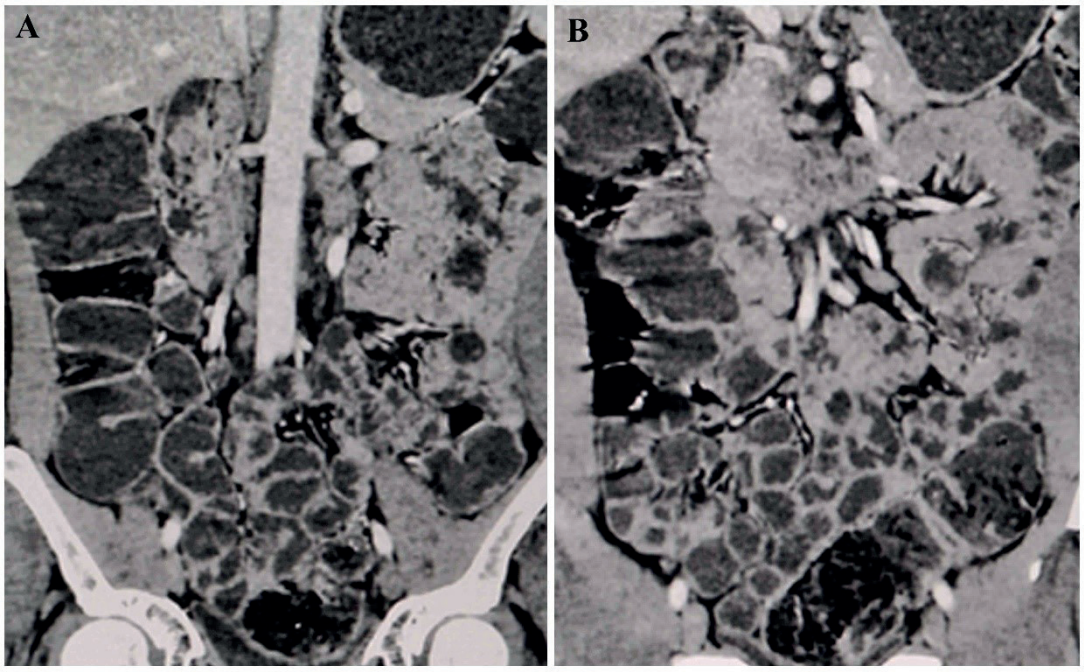

Figure 1 *CT enterography. Coronal images showing A: adequate luminal distention & uniform wall enhancement of normal jejunal and ileal loops, B: prominent mucosal pattern of normal jejunal loops.*

Materials and methods

This is a cross-sectional study with a two-year duration (September 2017-2019), with a study population comprising 105 patients presenting with bowel lesions in IMS & SUM Hospital, Bhubaneswar. Institutional Ethical Committee approval was obtained for the study. The radiological procedure was explained to the patients and obtained informed consent from all patients. While evaluating with MDCT (GE Optima CT660 128 slice with pressure injector), initially plain CT scan of the patient was done in the supine position. Mannitol was given 60-90 min before the contrast-enhancing CT image acquisition, as described in flow diagram (Figure 2). The post-contrast study was performed in dual phase/triphasic protocol after injecting approximately 100 mL water-soluble non-ionic iodinated intravenous contrast (350 mg% IOMERON). CTE images were analyzed to compare the diagnosis with the available histopathological and ultrasonography results. Patients in the age group of 10 to 85 years with complaints of fever, abdominal pain, nausea, vomiting, altered bowel habits, loss of appetite, and loss of weight were included in this study. Patients suspected of small bowel diseases and follow-up cases of small bowel diseases were included. The exclusion criteria were any suspected leak or perforation, postoperative studies, pregnancy, and patients with previous allergy history for intravenous contrast material use.

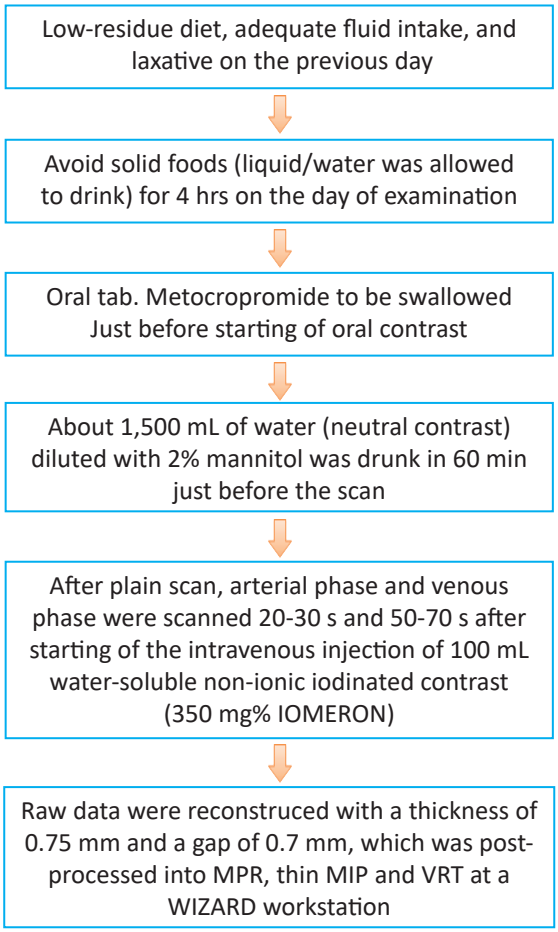

Figure 2 *Experimental flow diagram of CTE procedure.*

Statistical analysis

Quantitative data was represented using mean±SD or median with Interquartile range (IQR). The qualitative data was described in the form of frequency and percentage. The association among two qualitative variables was measured using the Chi-Square test. The diagnostic accuracy of MDCT imaging for small bowel lesions was also evaluated to detect abnormality in the patient. All associations were tested at a probability level of 0.05.

Results

The study population included 65 male and 40 female patients. The age of patients ranged from 10-85 years with a mean age of 42.3 years, while most were from the 40-49 years group (Figure 3). The luminal distension of the ileum, measured from outer wall to outer wall of the bowel loop, was adequate (≥2 cm) in 99% of cases using 2% mannitol as oral contrast.

Of the 105 patients studied, most had thickening of the jejunal loops (16.2%), followed by ileal thickening (14.3%). Ileum, caecum, and ileocecal junction were essential sites of wall thickening (13.3%). In patients with pathological wall thickening, most showed symmetrical wall thickening (53.3%), whereas asymmetrical wall thickening was seen only in 10.5% of patients. Patients with suspected bowel pathology had presented mucosal hyperenhancement of the distended bowel loops in 39% of patients, whereas

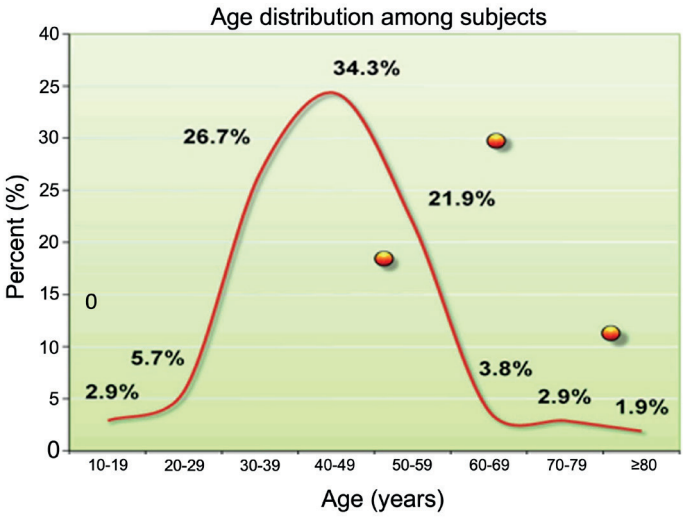

Figure 3 *Age distribution among the subjects (patients with small bowel diseases).*

it was absent in 61%. The mural stratification, i.e., target sign, was seen at the site of bowel pathology in 33.3% of patients, whereas 66.7% did not have any such finding. Around 61% of patients showed peri-bowel inflammatory changes at the site of bowel pathology, whereas it was absent in 39% of patients (Table 1).

Table 1 Prevalence of CTE features among the study population.

CTE feature	Study population (N=105)	
	Present (%)	Absent (%)
Symmetrical wall thickening	56 (53.3%)	49 (46.7%)
Asymmetrical wall thickening	11 (10.5%)	94 (89.5%)
Homogenous enhancement	54 (51.4%)	51 (48.6%)
Heterogenous enhancement	11 (10.5%)	94 (89.5%)
Mucosal hyperenhancement	41 (39.0%)	64 (61.0%)
Mural stratification	35 (33.3%)	70 (66.7%)
Peri bowel inflammation	64 (61.0%)	41 (39.0)

Most patients with suspected bowel diseases were diagnosed with ileocecal tuberculosis (11.5%), while 7.6% had small bowel inflammation (duodenitis, jejunitis, or ileitis) and 6.7% had presented with Crohn's disease. These three diseases formed the majority of diagnoses on CT enterography. Another group of 6.7% cases was diagnosed with small bowel neoplastic masses. Patients with small bowel obstruction (5.7%), including those having abdominal hernias with bowel as content (6.7%), were also encountered in the study. Small bowel diverticula, most commonly duodenal diverticula, was observed in 5.7% of patients. Pancreatic head masses with adjacent duodenal compression and invasion were observed in 5.7% of patients. Ischemic bowel disease (arterial or venous) was observed in 2.9% of patients. Strictures of small bowel narrowing with proximal bowel dilatation were observed

in 1.9% of patients. Small bowel intussusception was observed in 1.9% of patients, whereas ulcerative colitis was observed in 1.9%. Pyloric malignancy involving the proximal duodenum was also observed in 1.9% of patients. Other rare and miscellaneous observations were also made in the remaining patients, like necrotizing pancreatitis with jejunal involvement (1%), etc. (Table 2).

Table 2 Spectrum of small bowel diseases diagnosed on CTE.

Diagnosis	Number	Percentage
Ileocecal tuberculosis	12	11.5%
Abdominal hernia	7	6.7%
Crohn' s disease	7	6.7%
Generalized small bowel obstruction	6	5.7%
Pancreatic mass compressing and invading the duodenum	6	5.7%
Small bowel mass	7	6.7%
Jejunitis/duodenitis/Ileitis	8	7.6%
Ischemic bowel disease	3	2.9%
Adenocarcinoma of pylorus of stomach involving duodenum	2	1.9%
Ileo-ileal intussusception	2	1.9%
Small bowel diverticuli	6	5.7%
Small bowel stricture with proximal bowel dilatation	2	1.9%
Ulcerative colitis	2	1.9%
Miscellaneous	5	4.8%

Most patients diagnosed with bowel diseases related to jejunum had presented with jejunal wall thickening (>3mm). Thus, a statistically significant correlation is seen between jejunal wall thickening and bowel diseases diagnosed on CT enterography (p<0.001) using Pearson chi-square. The above table shows that most patients with CT diagnosis of bowel diseases and ileum as the site of suspected wall thickening had ileal wall thickening (>3mm). Thus, a statistically significant correlation is seen between ileal wall thickening and bowel diseases diagnosed on CT enterography (p<0.001) using Pearson chi-square.

Discussion

Various radiological features of small bowel diseases were evaluated using 2% mannitol for adequate small bowel distension and characterization of multiple small bowel diseases. The study population had a mean age of 42.3, with a distribution of males and females of 35.5% and 64.4%, respectively.[10] According to the study by Zhang LH *et al*. 2005 luminal distention of ileal loops was adequate and satisfactory in most of the normal volunteers, with the mean distention score being 2.52±0.22 cm, 2.81±0.31 cm, and 2.33±0.19 cm in duodenum, ileum, and jejunum respectively.[9] The small bowel distension was graded 0-3 (grade 0 was for no distension, while grade 3 was for optimal distension) by grading on the basis of diameters of ileum and jejunum.[11] Poor distension was observed in only 2 of the 107 patients. Most of the causes for symmetric wall thickening along the circumference of the bowel were benign in etiology. Crohn's disease and tuberculosis are common causes of such conditions, though they sometimes may cause asymmetric thickening.[12] At the same time, asymmetric wall thickening is evident in patients presenting with neoplasms. However, lymphomas sometimes can cause symmetric wall thickening.[9]

In our study, most patients with asymmetrical wall thickening were diagnosed with malignant abdominal masses (71.4%). In contrast, symmetrical wall thickening did not have abdominal mass as the diagnosis (98.1%). Lymphoma and intramural hemorrhage of the small bowel can cause noticeable thickening and homogenous mural enhancement.[13] A heterogeneous enhancement pattern is a typical characteristic of small intestinal neoplasms. It is also most common in adenocarcinomas and gastrointestinal stromal tumors (GIST). The enhancement pattern in GIST always depends upon its size, and small-sized tumors tend to be well-circumscribed and show homogenous enhancement.

In contrast, the large tumors present with more irregular morphology, ulcerated margin, and heterogeneous enhancement. Rarely, lymphomas may enhance heterogeneously.[14,15] The target appearance of an abnormal small intestinal segment indicates a benign process within the bowel wall. This abnormal appearance is due to mucosal and serosal enhancement with central low attenuation submucosa. Though it was specific to Crohn's disease, it could be observed in other conditions, such as ischemia, infection, radiation enteritis, hemorrhage, and angioedema.[16]

Limitations of the study

Although adequate bowel distension was achieved

in most patients, it was inadequate in some. The possible reason could be wrong and unsupervised drinking technique of the oral contrast by the patients, i.e., either drinking it very fast or too slow. Neutral oral contrast cannot differentiate between bowel loops and any postoperative collections as both will be fluid density.

Conclusion

In our study, using 2% mannitol as an additive and a negative oral contrast agent like water had shown excellent results for adequate small bowel distension. Hence by using this technique for the evaluation of various bowel pathologies, radiological features like patterns of wall thickening (symmetrical or asymmetrical) and wall enhancement (homogenous or heterogeneous) were better delineated with accuracy. Mucosal hyperenhancement, mural stratification and other mucosal details, and prominent vasa recta indicating active disease process in Crohn's disease were seen with greater details. As this technique can accurately diagnose bowel wall and mucosal details, including enhancement patterns and surrounding mesentery and lymph nodal accurately; mannitol based CTE is the modality of choice for diagnosis of the small bowel disease spectrum.

Conflicts of Interest

All the authors report no conflict of interest.

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Stroke health literacy: a narrative review of assessment tools and improvement strategies

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ABSTRACT

Background: Stroke is a serious life-threatening health condition. Prevention, treatment, and rehabilitation for stroke rely heavily on stroke health literacy, which refers to health literacy regarding stroke and stroke literacy.

Objectives: The objectives of this review were to investigate stroke health literacy and summarize into 3 main topics: 1) assessment tools for stroke health literacy; 2) stroke health literacy levels in various populations; and 3) strategies to improve stroke health literacy.

Materials and methods: A comprehensive search of the English literatures published between 2011-2021 was conducted using PubMed and Scopus databases. All studies relevant to stroke health literacy regardless the study types were included.

Results: Total of fourteen studies complied with the criteria were included in a review. As a results, nine assessment tools for stroke health literacy were found (four for health literacy and five for stroke literacy). Stroke health literacy was insufficient in the general population, the population at high risk for stroke, and patients with stroke. Some strategies to improve stroke health literacy were revealed, consisted of two stroke educational programs for patients with stroke and one educational program for the general population.

Conclusion: To conclude, there is very limited knowledge about stroke health literacy in terms of assessment tool, and improvement strategy. Further research is needed in order to expand knowledge and increase comprehension regarding stroke health literacy, and thus improve preventive, curative, and rehabilitative outcomes.

Introduction

Health literacy (HL) is the ability to access, understand, evaluate, and communicate information to promote, maintain, improve health in a variety of settings across the life course, and to apply health information to make appropriate health decisions.[1,2] HL hierarchy is built upon the degree of literacy in health, ranging from basic to advanced, namely, functional, communicative, and critical literacy.[3] Media literacy has been added in some studies based on the hypothesis that media also affect health perception and personal health management.[4] Inadequate HL leads to poor health knowledge, medication nonadherence, an inability to use health information for self-management and health service access, low disease prevention compliance, early health problem development, frequent hospitalization, and poor health outcomes.[5-7]

Stroke is the second leading cause of death and the third leading cause of disability.[8] Approximately 5.5 million people die from stroke each year, and more than 116 million years of healthy life are lost due to stroke-related mortality and disability.[8] The incidence of stroke is increasing,

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particularly in low- and middle-income countries. More than 13.7 million new strokes are estimated each year. Of these, almost 60% occur in people under 70 years of age.[8] Stroke is classified into three subtypes based on different causes: 1) ischemic stroke, 2) hemorrhagic stroke, and 3) subarachnoid hemorrhage stroke. Among these, ischemic stroke is the most common.[9] Some stroke survivors have consequences depending on the stroke type, severity, and brain lesion location, for example, motor control impairment, perceptual deficit, cognitive deficit, communication problems, and emotional problems. Long-term disability or some degrees of impairment usually persists, and rehabilitation is required to improve function, prevent further complications, and reduce possible health problems.

HL plays a crucial role in stroke prevention and rehabilitation. Sufficient HL lessens stroke severity and improves treatment and rehabilitation outcomes.[10] Stroke patients with adequate HL can access and use health information for self-management, rehabilitation compliance and the prevention of complications. Furthermore, stroke literacy, or specific knowledge regarding stroke, including stroke symptoms, stroke risk factors and appropriate response to the occurrence of stroke, is important in stroke prevention and care.[7,11-13] Poor stroke literacy leads to delayed hospital arrival and failure to provide proper stroke care.[11]

There were some studies regarding HL in stroke high-risk population in Thailand. The first study was one-group experimental research to examine the level of HL for stroke, before and after received HL development program among stroke high-risk group (hypertension patients) and their family caregivers. Contents of the development program in this study consist of stroke warning signs, stroke symptoms and access to emergency medical service. The result demonstrated a positive correlation between HL and health behavior both in stroke high-risk group and family caregivers. However, there was no significant correlation between HL of family caregivers and health behavior of stroke high-risk patients. These results lead to the conclusion that HL development program was effective in improving HL level and should be implemented in both current and new patients with hypertension.[14]

The second study was a research and development study, with aims to develop and evaluate the effectiveness of the HL development model for stroke prevention among stroke high-risk patients at primary care units. The developed model in this research consisted of four main processes: 1) promoting the cooperation of health team administrators and network partners in primary care units, 2) strengthening HL in preventing stroke of high-risk patients, 3) conducting continuously home visit by public health volunteers and caregivers, and 4) providing consultation and evaluation in provincial, district, and sub-district levels. After the experiment, the participants had higher HL score in stroke prevention, risk awareness, warning symptoms and preliminary risk assessment. The researchers then concluded that the provincial public health office and related agencies should provide sufficient resources as well as strengthen the health teams and network partners at the primary level.[15]

This narrative review aimed to investigate knowledge of stroke health literacy (SHL), which refer to the combination of HL regarding stroke and stroke literacy and summarized this knowledge into 3 main topics: 1) assessment tools for SHL; 2) SHL levels in patients with stroke, the population at high risk for stroke, and the general population; and 3) interventions to improve SHL and their effectiveness.

Materials and methods

A narrative review provides recent knowledge about specific topics without a description of methodological approaches.[16] The steps include 1) developing the research question, 2) identifying search terms, 3) identifying databases, 4) searching the literature, 5) evaluating the literature, 6) extracting data, 7) analyzing the data, and 8) interpreting and synthesizing the findings.

Data sources

A literature search was conducted using PubMed and Scopus databases. The search terms were "stroke/ cerebrovascular accident", "health literacy", and "stroke literacy". Only studies published in the English language between 2011 and 2021 were included.

Study selection

The first author screened the titles and abstracts (Figure 1). Articles not related to SHL, and duplicates were excluded. The first author reviewed the full-text articles and, in consultation with the second author, removed articles which did not meet the following inclusion criteria: 1) studied SHL, 2) were written in the English language, and 3) were published between 2011 and 2021.

Data extraction

Data were extracted from all included studies in order to summarize the variation and detail of each study. The first author and the second author developed the scopes for data extraction: study objectives, participants' characteristics, research context, assessment tools' characteristics, interventions, outcomes, strengths, and limitations. The first author extracted the data and discussed the results from data extraction with the second author.

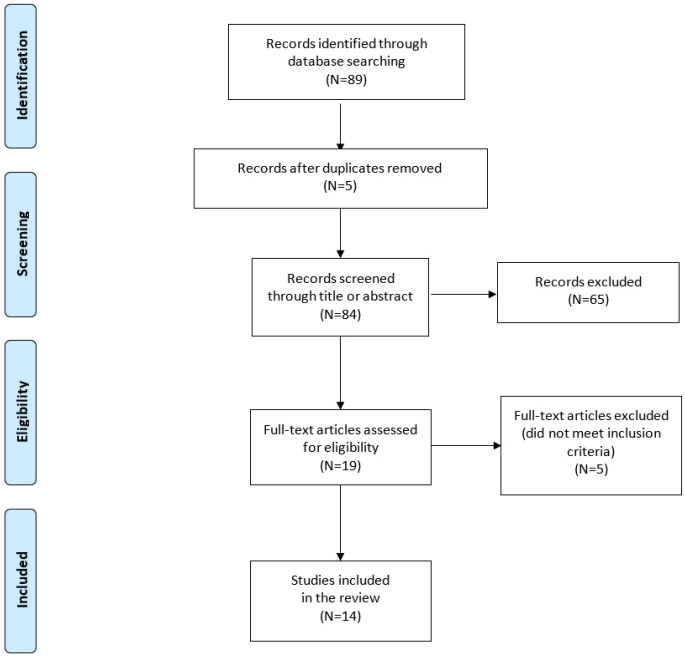

Figure 1 *Summary of study selection.*

Results

The initial search resulted in 89 articles. Of these, 5 were duplicates, and 65 were not related to SHL. After the exclusion of 5 additional articles due to unmet inclusion criteria, 14 articles were included in the review (Figure 1). Detailed descriptions of the characteristics and outcomes of the included studies were presented in Table 1.

Assessment tools for stroke health literacy

A total of nine assessment tools related to SHL were found, consisted of four tools for HI assessment, and five tools for stroke literacy assessment. Among the HL assessment tools, only one was specifically developed for stroke, while the rest were adapted from general HL assessment tools.

Health literacy assessment tools

The health literacy battery for three phases of stroke (HL-3S) was the only assessment tool developed specifically for patients with stroke.[21] HL-3S has three question categories: 1) health care tests for the acute phase (10 questions), 2) disease prevention tests for the subacute phase (10 questions), and 3) health promotion tests for the chronic phase (10 questions). Tests of the tool's psychometric properties with 422 stroke patients showed high validity and reliability. Findings from the principal component analysis (PCA) reported eigenvalues of the first component between 1.51-1.57, interitem residual correlations between 0.00-0.29 and Rasch reliability coefficients between 0.86-0.87. An advantage of the HL-3S is its appropriateness in assessing patients according to stroke phases.

There were three assessment tools that were adapted to assess HL in stroke patients: a Mandarin version of the short-form health literacy scale (SHEAL),[18] a Mandarin version of the European health literacy survey questionnaire (HLS-EU-Q),[10] and the health literacy assessment using talking touch screen technology (Health LiTT).[19] The original SHEAL comprises 11 multiple-choice items, of which 3 items are used for numeracy skill assessment and 8 items are used for comprehension ability assessment.[26] Huang et al. tested the Mandarin version of the SHEAL with 87 stroke patients.[18] It was found to be valid and reliable (Cronbach's alpha of 0.82). This instrument showed a high correlation with the Public Stroke Knowledge Quiz (PSKQ) (r coefficient of 0.62, $p<0.001$). The findings showed a ceiling effect, which limited the instrument's ability to distinguish the investigated variables in a high HL group. Therefore, the instrument needs further revision to improve its internal consistency reliability and discriminative validity, particularly in patients with high HL. Three years after the publication of the SHEAL study, the same authors tested the psychometric properties of a Mandarin version of the HLS-EU-Q in patients with stroke.[10] HLS-EU-Q comprises 47 questions with a Likert scale assessing patients' competencies to access, understand, appraise, and apply health information for health care, disease prevention, and health promotion. For the Mandarin version of the HLS-EU-Q, 311 patients with stroke completed the questionnaires. The findings showed a Rasch model fit with 12-domain structures. Huang et al.[10] recommended using the instrument to assess HL in patients with stroke. The last HL assessment tool used in patients with stroke was the health LiTT, a multimedia, self-administered test.[19] The original version of the health LiTT has 82 items. Hahn et al used a short form of the health LiTT comprising 16 items on prose, document, and quantitative health information.[19] The psychometric properties of this version were not described, although the original version of the health LiTT revealed validity and high reliability.[27]

Table 1 Summary of included studies.

Authors (year)	Objectives	Participants	Assessment tools	Result/Main outcomes
Stroke health literacy assessment in the general population				
Akiyama *et al*[17] (2013)	To assess stroke knowledge in the Japanese population	11,121 Japanese individuals from across Japan Mean age: 44.8 years (range 20-69 years)	Internet-based questionnaire survey	The respondents' knowledge of stroke was considered insufficient; knowledge was higher in older respondents than in younger respondents.
Lim *et al*[18] (2014)	To evaluate the level of stroke literacy in citizens of Singapore	687 Singaporean citizens and permanent residents living in a public housing estate Age ≥21 years, Mean age: 48 years	Interviews (face-to-face) using open-ended questions (modified SAQ)	Stroke literacy in the study population was poor, and there was a general lack of awareness of stroke symptoms and risk factors.
Rissado *et al*[19] (2018)	To investigate public stroke literacy in a South Brazilian city	633 normal subjects in a South Brazilian city Mean age: 55.3 years Mean education: 9.6 years	Questionnaires combined with closed- & open-ended questions	Stroke literacy in the South Brazilian city was not adequate.
Zafar *et al*[20] (2020)	To assess stroke literacy in the general population living in the Eastern Province of SA	1,213 respondents Age ≥15 years male 37.6%, female 62.4%	Structured questionnaire distributed through an electronic website over a period of 6 months	Stroke literacy in the population of the Eastern Province of SA was insufficient.
Stroke health literacy assessment in a population at high risk for stroke				
Rolls *et al*[21] (2017)	To investigate the relationships among anticoagulant knowledge, health literacy, and self- reported adherence in patients taking warfarin and DOACs	48 patients with AF Age ≥18 years Mean age: 76.4 years	AKT S-TOFHLA MMAS	Significant correlations were observed among health literacy, DOAC knowledge, and adherence.
Huang *et al*[22] (2015)	To validate a Mandarin version of the SHEAL in stroke patients	87 stroke patients Age ≥20 years, Mean age: 57 years Months after onset <6 months: 24 ≥6 months: 55	Interviews (face-to-face) using the SHEAL and PSKQ	The SHEAL has good psychometric properties and can be used to assess the health literacy of stroke patients for research purposes. However, for clinical context, the SHEAL should be used with caution.
Hahn *et al*[23] (2017)	To evaluate and compare functional literacy, health literacy, fluid cognitive function, and self-reported health in individuals with SCI, stroke, and TBI who live in community dwellings.	209 people with SCI, Mean age: 46 years 184 TBI, Mean age: 40 years 211 Stroke, Mean age: 56 years	Health LiTT WRAT-4	Strong correlations were observed among functional literacy, health literacy, and fluid cognitive function. Higher health literacy was associated with better mobility, less anxiety, and better overall health.
Wang *et al*[24] (2018)	To survey stroke knowledge and influencing factors among people with acute ischemic stroke at discharge in Hubei Province, China	1,531 AIS patients Age ≥18 years Mean age: 65.2 years	Interviews at discharge with a questionnaire.	Most AIS patients had insufficient knowledge at discharge.
Huang *et al*[25] (2018)	To examine the validity of the HLS-EU-Q in patients with stroke using Rasch analysis	311 stroke patients Age ≥20 years Mean age: 59.7 years Median after onset: 9 months	The Mandarin version of the HLS-EU-Q	The HLS-EU-Q (12-domain) is a valid measurement tool for clinicians and researchers to assess health literacy in patients with stroke.
Huang *et al*[26] (2020)	To develop a health literacy battery for three phases of stroke	442 stroke patients Age ≥20 years Mean age: 61.5 years	HL-3S	The HL-3S has a good construct validity and Rasch reliability.
Stroke health literacy interventions				
Williams *et al*[27] (2012)	To assess the effectiveness of child-mediated stroke communication or HHS regarding stroke literacy improvement in parents of children enrolled in an HHS program	71 parents 182 children Age 9-12 years	Stroke Literacy Questionnaire	Parental stroke literacy improved after the program; HHS may be effective as a tool for improving parental stroke literacy.

Table 1 Summary of included studies. (continued)

Authors (year)	Objectives	Participants	Assessment tools	Result/Main outcomes
Stroke health literacy interventions				
Sanders *et al*[28] (2014)	To examine the relationship between health literacy and stroke education outcomes	100 AIS patients males: 57 females: 43 Age ≥60 years: 48% <60 years: 52%	S-TOFHLA SPER	A clear relationship was observed between health literacy and stroke education outcomes.
Denny *et al*[29] (2017)	To assess changes in stroke knowledge,self-efficacy, and satisfaction before and after the intervention.	93 stroke patients in acute hospitals AIS: 65 ICH: 28	10-item questionnaire (written at a 4th grade reading level)	A significant increase was seen in stroke knowledge that lasted until the 30th day after following up. The stroke video intervention served as an adjunct to the verbal and written stroke education.
Szmuda *et al*[30] (2020)	To evaluate the quality, reliability, and audience engagement of stroke-related videos published on YouTube	101 English YouTube videos	DISCERN instrument VPI	Quality of YouTube videos is fair, and the videos can be used as a useful source of stroke information for patients and families.

Note: HHS; hip hop stroke, SAQ: stroke awareness questionnaire, S-TOFHLA: short form of the test of functional health literacy in adults, SPER: stroke patient education retention, SHEAL: short-form health literacy scale, PSKQ: public stroke knowledge quiz, AIS: acute ischemic stroke, ICH: intracerebral hemorrhage, AF: atrial fibrillation, SCI: spinal cord injury, TBI: traumatic brain injury, Health LiTT: health literacy assessment using talking touchscreen technology, WRAT-4: wide range achievement test, 4th edition, DOACs: direct acting oral anticoagulants, AKT: anticoagulation knowledge tool, MMAS: Morisky medication adherence scale, HLS-EU-Q: health literacy survey European questionnaire, MMSE: mini–mental state examination, SA: Saudi Arabia, VPI: video power index, HL-3S: health literacy battery for three phases of stroke.

Stroke literacy assessment tools

A search result revealed ten studies regarding assessment tools, consisted of assessment tools for healthy populations (four articles), populations at risk (one article), and patients with stroke (one article). The assessment tools for healthy populations ask participants about stroke symptoms, stroke risk factors, stroke management, and sources of information.[7,11-13] Questions to assess stroke literacy are either open-ended,[11] or a combination of both open-ended and closed-ended.[12-13] Data collection methods in these four studies included internet-based surveys,[7,13] and face-to-face interviews.[11-12] Only one article assessed stroke knowledge in the population at high risk for stroke (patients with atrial fibrillation).[17] In this study, the authors used the anticoagulation knowledge tool (AKT) and the short form of the test of functional health literacy in adults (S-TOFHLA) to evaluate the level of anticoagulant knowledge and HL, respectively. AKT was developed to assess knowledge about anticoagulants.[28] AKT comprises 25 items for direct acting oral anticoagulant users and 35 items for warfarin users. The original version has 28 items. The authors did not describe validity and reliability of modified AKT. S-TOFHLA is a tool with good reliability and validity for assessing functional HL. The test items consist of 4 numeracy items and 2 prose passages. With a maximum score of 36, a score of 23 and above is considered to indicate adequate HL, while a score of 22 or less is considered to indicate inadequate HL.[29] One article assessed stroke literacy in patients with stroke.[20] The studied instrument comprises 25 questions on common sense, warning signs, risk factors and dos-and-do nots after treatment. Testing the instrument with 25 patients with stroke, the authors reported high reliability of the entire scale (Cronbach's alpha of 0.95) and the four domains (Cronbach's alphas of 0.81, 0.89, 0.91 and 0.90). Factor analysis confirmed an item structure with 63% cumulative variance.

Stroke health literacy level

Of seven articles reporting levels of SHL, four, one and two studied the general population, the population at high risk for stroke, and patients with stroke, respectively. Overall, ordinary people, people at risk of stroke, and patients with stroke had inadequate SHL. For example, in Japan, less than half of respondents were confident about their stroke knowledge.[7] Only 2.3% believed they could identify stroke symptom when it occurred. In Brazil, approximately one-third of respondents did not understand the meaning of stroke (abbreviated in Portuguese as AVC for “acidente vascular cerebral”), and 50% did not know the warning signs.[12] These findings were similar to those of study surveys in Saudi Arabia[13] and Singapore.[11] Specific areas in which inadequate stroke knowledge was found included the following: facial asymmetry as a stroke symptom, diabetes and dyslipidemia as stroke risk factors, use of recombinant tissue plasminogen activator (rt-PA) and early rehabilitation as effective stroke treatment, and the nearest health care center for stroke management.

A study in a population at high risk for stroke reported lower AKT scores in patients with good medication adherence than in their counterparts with poor medication adherence.[17] HL was correlated with anticoagulant knowledge but not associated with medication adherence. According to the small sample size in this study (48 patients), the effect size was too small to be generalized. For patients with stroke, two studies reported inadequate HL in stroke patients. Approximately half of discharged patients with stroke did not know about stroke symptoms, and more

than half were unaware of risk factors (such as hypertension and smoking).[20] Another study reported that patients with stroke had the lowest HL score compared to patients with spinal cord injury and patients with traumatic brain injury (mean T-score of 53.6 vs. 58.1 and 57.8, respectively).[19]

Interventions to improve stroke health literacy and effectiveness

In-hospital stroke educational programs for patients with stroke

Two articles reported stroke educational outcomes.[23-24] Sander et al.[23] measured educational outcomes after patients had participated in stroke education covering the following topics: personal risk factors for stroke, stroke warning signs, activation of emergency medical services, need for follow-up after discharge, and medications prescribed for stroke prevention.[2] The session lasted 30 to 60 minutes. The participants answered five open-ended questions and completed the S-TOFHLA. The mean score for stroke knowledge was 6.7 out of 10. Patients with inadequate HL had the lowest stroke knowledge compared to those with marginal and adequate HL. In other words, the stroke educational program in this study was ineffective in patients with inadequate HL.

In another study, a five-minute stroke education video was shown to patients with acute ischemic stroke and intracerebral hemorrhage.[24] Input from stroke survivors, caregivers, and a multidisciplinary team was received during the creation of the video content. The authors used a video script with a 6th grade reading level. The patients completed ten-item questionnaires written at a 4th grade reading level before, immediately after, and 30 days after watching the video. The findings showed an increase in the median knowledge score before and after watching the video (median of 6 vs. 7 for both immediately after and 30 days after). A significant proportion of patients recognized stroke symptoms immediately after the video, and knowledge was retained 30 days later. Almost three-quarters of patients were satisfied with the video.

Stroke educational programs for general populations

One article reported stroke educational programs for the general population, and another assessed the quality of stroke education videos from YouTube. William et al.[22] developed a school-based stroke educational program called "Hip Hop Stroke" (HHS) for children aged 9 to 12 years to communicate stroke knowledge with their parents. The children attended one-hour sessions to learn hip hop for three days. They watched two four-minute cartoon music videos and read a comic book with their parents at home. The media was professionally produced and included age-appropriate stroke knowledge. Children also placed an HHS magnet on their refrigerators. Parents completed a stroke knowledge questionnaire before and one week after the intervention. The findings showed that parents' stroke knowledge (stroke symptoms, urgent action plan, and FAST mnemonic) increased significantly after the intervention.

One article assessed the quality of YouTube videos providing stroke education. The authors analyzed 101 videos containing at least one of the following search terms: stroke, brain attack, hemorrhagic stroke, ischemic stroke, and transient ischemic attack. An analysis with the validated DISCERN instrument found that the quality of the videos was fair. Two-thirds of the videos were of professional quality (uploaded by hospitals, narrated by doctors, and included stroke symptoms). Only 14.85% of these videos mentioned risk factors for treatment.[25]

Discussion

This narrative review explored up-to-date knowledge about SHL assessment tools and levels of SHL in the general population, the population at risk of stroke, and patients with stroke. Only 14 articles regarding this area were found, while there were six systematic review articles on HL and type-2 diabetes.[30] There was only one SHL assessment tool developed specifically for patients with stroke, while the rest were adapted from standard HL assessment tools or were for stroke knowledge assessment. SHL was inadequate in the general population, the population at risk for stroke, and patients with stroke. Stroke education programs were effective for both the general population and patients with stroke.

The quality of the assessment tool affects the completeness and accuracy of the measurement outcome. In this review, only four articles reported assessment tools for HL in patients with stroke. One was developed specifically for patients with stroke, and the rest were adapted from general HL assessment tools. These tools were valid and reliable; however, implementation of this tools was not found in other study. Stroke literacy is different from HL for stroke. The first refers to knowledge about stroke, such as stroke symptoms and stroke warning signs,[7,11,13] while the latter refers to people's abilities to obtain, understand, and use health information to make informed decisions about their health and health care.[31] Unlike assessment tools for HL in patients with stroke, various assessment tools for stroke literacy were found, but validity and reliability were reported in only few articles. Developing assessment tools for HL is challenging particularly for topics relating to stroke.[32] It requires a theoretical understanding of HL and a clinical context of stroke. The conditions of patients with stroke vary which may explain the paucity of research on HL for stroke.[21] A shortage of SHL measurement tools was one key finding. This review found three studies that modified tools originally designed for the general population and then used them in stroke populations.[10,18,26] Even though all tools were shown to have some good psychometric roperties, retesting of validity and reliability is still required when they are implemented in different contexts, particularly when the targeted population differs from the study population. In this review, only one study developed a novel, specific measurement tool for the stroke population.[21] For this reason, HL measurement tools with good psychometric properties and specifically designed for stroke populations need to be further developed.

All articles in this review reported inadequate SHL in the general population, the population at high risk for stroke, and patients with stroke. Inadequate HL is associated

with poor understanding of medical information, adverse health outcomes, and undesirable health effects.[31] It is a concern that the general population with inadequate SHL has a higher risk of stroke and that stroke patients with inadequate SHL have poorer treatment outcomes than their counterparts with adequate SHL. For example, a lack of knowledge about warning symptoms of stroke and health service providers for stroke in an area can result in delayed treatment and poor treatment outcomes. Unfortunately, none of the articles in this review reported an association between SHL and health outcomes. Thus, future research to examine this association are needed. Factors associated with inadequate SHL vary depending on diseases and conditions. For example, cognitive impairment decreases stroke patients' ability to comprehend health information, and physical disability in stroke patients limits their accessibility to health care services. From the review, limited knowledge regarding factors associated with SHL was found, and further study in this area is required.

Improving HL is crucial to prevent stroke, both in the general population and patients with stroke, and promote recovery from stroke attack. Similar to this review, Visscher et al.[33] found that most interventions to improve HL were focused on the functional level - the lowest level of HL. People with a functional level of HL can obtain information from health resources but cannot use information to communicate with other people, including health professionals.[3] The primary objective of HL interventions is to empower patients to move from passive to active and become critical players in health care. Articles in this review failed to demonstrate such improvement in participants. A comprehensive HL intervention model provides a comprehensive approach to developing HL interventions based on a complex HL concept.[34] This model targets individuals, individuals with inadequate HL, communications between individuals and health professionals, health professionals, and health service barriers.

This review has some limitations. Firstly, the inclusion of only studies published in English may have limited the results from relevant studies written in other languages. Secondly, restricted searching term to "health literacy" and "stroke literacy" but not include other similar term such as "stroke knowledge" or " stroke awareness", may limited other relevant studies. Thirdly, the inclusion of all relevant studies regardless of their quality biased the interpretation of findings. However, this was considered necessary, as there are still limited studies in this area. Finally, the article search in this review was not exhaustive, and relevant articles not published in PubMed and Scopus were not included in this review.

Future directions

Stroke educational campaigns have been proved to be an effective method to improve knowledge and awareness regarding stroke.[35] Therefore, stroke educational campaigns can be implemented as one intervention strategy to improve HL in patients with stroke. In term of assessment, we found a lack of clinical implications of assessment tools for HL in patients with stroke. HL is linked to medical adherence and health outcomes. Therefore, HL assessment with valid and reliable tools should be performed in clinical practice to assess HL in patients with stroke before and after educating patients. Moreover, strong research designs are needed to develop assessment tools and evaluate the effectiveness of HL interventions.[32]

Conclusion

This review presents updated knowledge on SHL. This knowledge is very limited; however, the review showed 1) various validated and reliable tools to assess SHL; 2) inadequate SHL in the general population, the population at high risk for stroke, and patients with stroke; and 3) interventions to improve SHL. Further research on SHL is needed in order to expand knowledge and comprehension regarding stroke health literacy, and thus improve preventive, curative, and rehabilitative outcomes.

Ethical approval

Ethical approval and patient consent were not required since the present study was a narrative review of previously published literature.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Instructions for Authors

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General Principles

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PLEASE be informed that references of books and chapter in edited book should not be include in the research article, but others manuscript categories.

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Journal History

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