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Original Article **Open Access**

Factors Associated with Distant Metastasis from Cutaneous Melanoma: A Study at Maharaj Nakorn Chiang Mai Hospital

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ABSTRACT

OBJECTIVE Cutaneous melanoma is an aggressive tumor associated with high mortality, particularly in the advanced stages. The objective of this study is to identify risk factors for distant metastasis in melanoma patients.

METHODS This retrospective analytical study included all patients diagnosed with cutaneous melanoma and treated at Maharaj Nakorn Chiang Mai Hospital between January 2002 and July 2019.

RESULTS One hundred and forty patients were enrolled in the study. Distant metastasis was found in 45% of the patients (n = 63) and the most common site was the lung (27.9%, n = 39). Multivariable analysis detected two significant prognostic factors for distant metastasis: Breslow thickness 2-4 mm and > 4 mm (p = 0.048 and 0.045, respectively) and nodal metastasis (p < 0.0001).

CONCLUSIONS Breslow thickness > 2 mm and nodal metastasis are associated with distant metastasis and the lung is the most common site of distant metastasis. The patients found to be at risk should be aggressively investigated for distant metastasis.

KEYWORDS melanoma, skin cancer, distant metastasis, risk factor, nodal metastasis, Breslow thickness

INTRODUCTION

Cutaneous melanoma is a cancer originating from melanocytes. Estimates of the global incidence and mortality of cutaneous melanoma in 2018 indicated that the age-standardized incidence in South-Eastern Asia was 0.46 per 100,000 patient-years in males and 0.40 per 100,000 patient-years in females, while in the United States, the incidence of melanoma was 19.7 per 100,000 population (1). The disease is an aggressive tumor with high mortality in the advanced stages and the highest mortality rate of cutaneous malignancy (2).

A study by Carolina et al. in a Brazilian population reported that of patients who had no metastasis when diagnosed, during follow-up metastasis had occurred in 26% of cases. Factors associated with metastasis are male gender, nodular melanoma, Breslow thickness > 4 mm and ulceration (3). Patients with metastasis had a 5 year survival rate of less than 15% (4). The primary organ of distant metastasis is an important factor in the survival rate (5). In melanoma with metastasis, the average survival periods in patients with metastasis in 1, 2, or 3 or more organs are 7 months, 4 months and 2 months, respectively, and the 1-year survival rates are 36%, 13% and less than 1%, respectively. The site of organ metastasis also affects survival. Metastasis in the brain and liver shows a median survival of 4 months; where there is metastasis into the skin and lymph nodes there is a median survival rate of 15 months (6).

Staging of melanoma is based on the system described in the AJCC 8th edition. The criteria include the depth of melanoma proliferation invasion, metastasis to lymph nodes and distant metastasis to other organs. If diagnosis is made at an early stage, wide excision of the tumor is usually sufficient, resulting in a high survival rate. However, cutaneous melanoma is an aggressive tumor with a trend of metastasis to distant organs. In the advanced stages, surgery is often unsuccessful, and the disease becomes very difficult to treat (7).

The long-term prognosis in cutaneous melanoma with metastasis is poor with a mean survival rate after treatment with immunotherapy such as Ipilimumab of between 8 and 12 months. Combined treatment of surgery, chemotherapy, immunotherapy and radiotherapy may increase the mean survival rate many years (8).

There have been few studies of cutaneous melanoma in Thailand to date and no studies have been conducted at Maharaj Nakorn Chiang Mai Hospital.

OBJECTIVES

The main purpose of this study is to research the factors related to distant metastasis of cutaneous melanoma. The secondary objectives of this study are to consider factors related to lymph node, lung and brain metastasis and disease-free survival of cutaneous melanoma metastasis.

METHODS

This retrospective study was conducted by collecting data on factors affecting distant metastasis of cutaneous melanoma including primary sites of cutaneous melanoma, histopathological characteristics, and the time between no metastasis and distant metastasis.

Inclusion criteria

1. Patients who had been diagnosed with or treated for cutaneous melanoma and had been followed up at Maharaj Nakorn Chiang Mai Hospital from 1 January 2005 to 31 July 2019.

2. Availability of histopathology studies confirming diagnosis of cutaneous melanoma.

Exclusion criteria

1. Patients who had no histopathology studies.

2. Patients who had been diagnosed with other malignancies which were being treated or which were not in remission.

Population

The number of subjects required for the study was calculated following the study "Prognostic factors for metastasis in cutaneous melanoma". If the distant metastasis of cutaneous melanoma is 0.263 (26.3%), risk of distant metastasis of cutaneous melanoma from the expected factor of 2.5-3 times with a 95% confidence interval, an 80% power of the test required a sample size in the range of 110-158 patients (3).

Data collection

Data collected included: 1) basic data on cutaneous melanoma patients (gender, age, date of diagnosis); 2) primary site of the cutaneous melanoma; 3) histopathology study results including subtype of cutaneous melanoma, Breslow thickness, Clarke level, ulceration, and tumor infiltrated lymphocytes; 4) lymph node metastasis, distant metastasis and organ(s) of the disease metastasis; 5) date the first distant metastasis was detected and the first organ(s) of distant metastasis; 6) date of onset of signs and symptoms of cutaneous melanoma, and 7) date lost to follow-up or death.

Statistical analysis

Descriptive data (gender, primary site of cutaneous melanoma, clinicopathological subtypes, Clark level, Breslow thickness, ulceration, mitotic index, lymphocyte infiltrate, *BRAF* 600, other organ metastasis) are presented as percentages; continuous variables (age) are presented as mean and standard deviation. The Kaplan-Meier method is used for survival analysis of the interval from occurrence of metastasis in patients with cutaneous melanoma according to lymph node metastasis and Breslow thickness. Univariate analysis and multivariable analysis of the risk factors of melanoma metastasis to distant organs and the risk factors for melanoma metastasis to lymph nodes, lung, and brain using Cox regression with penalized likelihood for factors related with metastasis was conducted. A p-value < 0.05 was considered statistically significant.

All statistical analyses were carried out using SPSS version 23.0.

This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (MED-2561-05770).

Definitions

Cutaneous melanoma is a skin cancer that originates from melanocytes. Breslow thickness is the thickness of the melanoma measured from the top of the granular cell layer of the epidermis to the deepest point of melanoma invasion. Clark level is a 5-stage system describing the depth of invasion by the melanoma into the skin. Nodal metastasis is where there is metastasis of the melanoma into the lymph nodes. Distant metastasis is the metastasis of the melanoma to distant organs. Disease-free survival is the period during which the cancer is in remission.

RESULTS

One hundred and forty patients were diagnosed with melanoma at Maharaj Nakorn Chiang Mai Hospital between 1 January 2005 and 31 July 2019. Seventy-two were male (51.4%) and 68 female (48.6%). The average age of the patients was 60.88 ± 14.42 years. The primary sites were hands and feet in 101 cases (2.1%), lower extremities in 12 cases (8.5%), trunk in 12 cases (8.5%), head and neck in 10 cases (7.1%) and upper extremities in 5 cases (3.5%) (Table 1). The mean time interval from diagnosis of first-ever melanoma to distant metastasis was shown in Appendix.

The histopathologic subtypes were nodular melanoma in 57 cases (40.7%), superficial spreading melanoma in 44 cases (31.4%), acrolentiginous melanoma in 35 cases (25.0%), desmoplastic melanoma in 2 cases (1.4%), and lentigo maligna in 2 cases (1.4%). The most common depth of tumor invasion by Clark level was Clark level IV in 64 cases (45.7%) and by Breslow thickness was Breslow thickness > 4 mm in 92 cases (65.7%). Other findings include ulceration in 85 (60.7%) and no ulceration in 12 cases (8.6%), tumor infiltrated lymphocytes in 17 cases (12.1%), and no tumor infiltrated lymphocytes in 8 cases (5.7%) (Table 1).

After follow-up treatment, regional lymph node metastasis was present in 110 cases (78.6%), distant metastasis in 63 cases (45%), lung metastasis in 39 cases (27.9%), brain metastasis in 16 cases (11.4%), liver metastasis in 13 cases (9.3%), bone metastasis in 8 cases (5.7%) and gastrointestinal metastasis in 5 cases (3.6%).

Primary outcomes

Multivariable analysis indicated that the risk factors Breslow thickness > 2 mm (p = 0.045) and regional lymph node metastasis (p < 0.0001) were statistically significantly related to distant metastasis (Table 2).

Breslow thickness greater than 4 mm was associated with an increased risk of distant metastasis of 3.45 times (p = 0.018, HR = 3.45) compared to a Breslow thickness less than 2 mm Multivariable analysis found that a Breslow thickness greater than 2 mm was significantly associated with distant metastasis of melanoma with a statistical significance of p = 0.048, HR = 2.98.

Metastatic invasion of the melanoma into the regional lymph nodes increased the risk of distant metastasis by 48.52 times compared to no nodal metastasis ($p \leq 0.0001$, HR = 48.52). Regional lymph node metastasis was statistically significantly associated with distant metastasis of melanoma ($p \leq 0.0001$, HR = 59.99).

Desmoplastic melanoma increased the risk of distant metastasis by 4.6 times compared to superficial spreading (p = 0.044, HR = 4.6) but the association was not statistically significant. Microscopic ulceration increased the risk of distant metastasis by 3.56 times (p = 0.034, HR = 3.56) compared to no ulceration, but the association was not statistically significant.

Gender, primary site of cutaneous melanoma, mitotic rate and *BRAF* mutation did not show any statistically significant association with distant metastasis of cutaneous melanoma.

Secondary outcomes

The risk factor associated with lymph node metastasis was a Breslow thickness greater than 4 mm (p = 0.027, HR = 2.12), while the risk factor associated with lung metastasis was regional lymph node metastasis ($p \leq 0.0001$, HR

Table 1. Patient characteristics

Characteristic	N = 140
Variable	Number (%)
Age	
Age mean±SD (year)	60.88 ± 14.42
Gender	
Male	72 (51.4)
Female	68 (48.6)
Site	
Head and neck	10 (7.1)
Trunk	12 (8.5)
Upper limbs	5 (3.5)
Lower limbs	12 (8.5)
Acral	101 (72.1)
Clinicopathological subtype	
Superficial spreading	44 (31.4)
Nodular	57 (40.7)
Acrolentigenous	35 (25.0)
Lentigo maligna	2 (1.4)
Desmoplastic	2 (1.4)
Clark level	
I	2 (1.4)
II	7 (5.0)
III	18 (12.9)
IV	64 (45.7)
V	49 (35.0)
Breslow thickness	
< 1 mm	7 (5.0)
1 - 2 mm	12 (8.6)
2 - 4 mm	29 (20.7)
> 4 mm	92 (65.7)
Ulceration	
Present	85 (60.7)
Not present	12 (8.7)
Mitotic index	
0	7 (5.0)
1 - 4	27 (19.3)
5 - 10	25 (17.9)
≥ 11	14 (10.0)
No information	67 (47.9)
Lymphocyte infiltrate	
Present	17 (12.1)
Not present	8 (5.7)
No information	115 (82.1)
BRAF 600	
Positive	8 (5.7)
Negative	2 (1.4)
Not investigate	130 (92.9)
Nodal metastasis	
Present	110 (78.6)
Not present	27 (19.3)
No information	3 (2.1)
Distant metastasis	
Present	63 (45.0)
Not present	77 (55.0)
Lung metastasis	
Present	39 (27.9)
Not present	101 (72.1)
Liver metastasis	
Present	13 (9.3)
Not present	127 (90.7)
Bone metastasis	
Present	8 (5.7)
Not present	132 (94.3)
Brain metastasis	
Present	16 (11.4)
Not present	124 (88.6)
GI metastasis	
Present	5 (3.6)
Not present	135 (96.4)

= 32.07). Multivariable analysis indicated that the presence of regional lymph node metastasis was a risk factor statistically significantly associated with lung metastasis ($p \leq 0.0001$, HR = 59.99) (Table 3).

A risk factor that showed a statistically significant association with brain metastasis according to the multivariable analysis was the presence of an acral lesion which reduced the risk of brain metastasis by 0.14 times ($p = 0.037$, HR = 0.014) compared to lesions on the head and neck. Lentigo maligna increased the risk of brain metastasis by 38.14 times ($p = 0.009$, HR = 38.14) compared to superficial spreading. Multivariable analysis showed that lentigo maligna increased the risk of brain metastasis by 4.48 times (Table 3).

Analysis of disease-free survival

Statistical analyses of disease-free survival were conducted using the Kaplan-Meier method and the log-rank test based on factors affecting distant metastasis of cutaneous melanoma found statistically significant association with Breslow thickness greater than 2 mm ($p = 0.048$) and regional lymph node metastasis ($p < 0.0001$) (Figures 1, 2).

DISCUSSION

Cutaneous melanoma is an aggressive tumor with a high mortality rate. In Thailand, the incidence of cutaneous melanoma is 0.1-0.4 per 100,000-person years, which is less than in Western countries (Switzerland (20.3:100,000

Table 2. Analysis of risk factors for metastasis of melanoma to distant organs including Cox regression with penalized likelihood multivariable analysis

Variables	Univariate analysis			Cox regression with penalized likelihood		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Clinicopathological type						
Superficial spreading	Ref.			Ref.		
Nodular	1.46	0.79 - 2.69	0.222	0.73	0.38 - 1.44	0.360
Acrolentigenous	1.52	0.75 - 3.08	0.245	1.07	0.51 - 2.21	0.860
Lentigo maligna	0.89	0.12 - 6.73	0.912	5.78	0.52 - 39.95	0.132
Desmoplastic	4.60	1.04 - 20.30	0.044	2.26	0.43 - 7.81	0.290
Breslow thickness						
< 1 - 2 mm	Ref.			Ref.		
2 - 4 mm	2.80	0.93 - 8.44	0.067	2.98	1.01 - 11.58	0.048
> 4 mm	3.45	1.24 - 9.64	0.018	2.77	1.02 - 10.33	0.045
Ulceration						
Present	3.56	1.10 - 11.48	0.034	0.97	0.35 - 3.64	0.954
Not present	Ref.			Ref.		
Nodal metastasis						
Present	48.52	6.98-6127.28	0.000	59.99	6.96- 8176.44	0.000
Not present	Ref.			Ref.		

CI, confidence interval; HR, hazard ratio; ref., reference group

Table 3. Analysis of risk factors for metastasis of melanoma to lymph nodes, lung, brain with Cox regression with penalized likelihood multivariable analysis

	Univariate analysis			Cox regression with penalized likelihood		
	HR	95% CI	*p*-value	HR	95% CI	*p-value*
Nodal metastasis						
Breslow thickness						
< 1 - 2 mm	Ref.					
2 - 4 mm	1.59	0.77 - 3.26	0.207	1.40	0.66 - 2.97	0.379
> 4 mm	2.23	1.18 - 4.21	0.014	2.12	1.09 - 4.13	0.027
Lung metastasis						
Nodal metastasis						
Present	32.07	4.54 - 4062.14	0.000	27.96	3.77 - 3577.56	0.000
Not present	Ref.					
Brain metastasis						
Site						
Head and neck	Ref.			Ref.		
Trunk	0.46	0.110 - 2.116	0.302	0.365	0.049 - 3.398	0.347
Upper limbs	0.12	0.001 - 1.307	0.088	0.068	0.000 - 1.293	0.075
Lower limbs	0.19	0.018 - 1.175	0.074	0.267	0.018 - 3.120	0.275
Acral	0.14	0.041 - 0.563	0.009	0.104	0.015 - 0.859	0.037
Clinicopathological type						
Superficial spreading	Ref.					
Nodular	1.39	0.442 - 4.920	0.576	1.020	0.319 - 3.694	0.973
Acrolentigenous	1.38	0.309 - 5.699	0.652	1.647	0.329 - 8.154	0.530
Lentigo maligna	7.23	1.255 - 32.823	0.030	4.279	0.417 - 37.761	0.210
Desmoplastic	5.03	0.037 - 50.677	0.380	2.481	0.016 - 57.604	0.620
Nodal metastasis						
Present	4.84	1.16 - 44.73	0.027	6.510	1.445 - 64.912	0.012
Not present	Ref.			Ref.		

CI, confidence interval; HR, hazard ratio; ref., reference group

cases per year), the Netherlands (19.4:100,000 cases per year), Denmark (19.2:100,000 cases per year), Norway (18.8:100,000 cases per year), and Sweden (18.0:100,000 cases per year)) (9).

One hundred and forty cases of malignant melanoma confirmed by histopathology between 1 January 2005 and 31 July 2019 were included in the study. We found that a Breslow thickness greater than 2 mm and regional lymph node metastasis were important risk factors related to distant metastasis. Deeper melanoma invasion showed a greater risk of distant metastasis (p = 0.048 for Breslow thickness 2-4 mm and p = 0.045 for Breslow thickness > 4 mm) (10), a finding that adds weight to reports in previous studies. Increased depth of melanoma invasion has been demonstrated to cause invasion into blood vessels and then metastasis to distant organs (11). Brauer et al. reported that increased depth of invasion heightened the risk of rapid metastasis and spread to lymph nodes (12).

Our study found that gender was not a risk factor for melanoma metastasis. Interestingly Pollack et al. determined that male was a significant risk factor for melanoma metastasis which reduced survival rates by 1 to 5 years (13). de Vries et al. found that males faced a greater risk of death from melanoma than females by a factor of 1.87 (14). Mervic et al. followed up 7,338 melanoma patients and found that females had a lower risk of distant metastasis than males (15). The cause of the greater incidence of metastasis in males is not obvious. It may be that females are more likely to react more rapidly to body changes rather than being related to male or female chromosomes or sex hormones. Some studies reported that oxygen free radicals are related to abnormal development of melanocytes that cause melanoma (16).

Patients with desmoplastic melanoma have a 4.6 times higher risk of metastases compared to patients with the superficial spreading subtype. The characteristics of desmoplastic melanoma are different from other types. The appearance of desmoplastic melanoma, a pale nodule, often does not immediately appear serious and thus results in delays in seeking treatment and diagnosis, while the pathological characteristics are similar to soft tissue sarcoma (17).

We found that ulceration increased the risk of cancer spreading by 3.56 times when compared to no ulceration (p = 0.034, HR = 3.56), but the multivariable analysis indicated no statistical significance. A previous study determined that ulceration was related to a negative prognosis including reduced disease-free survival (18). Balch et al. found that ulceration decreased the 5-year survival rate from 80% to 5%. Ulcerated lesions show greater thickness and are more likely to be related to a nodular growth pattern (19).

Our study also found that the primary site of the melanoma, mitotic rate, and *BRAF* mutation were not statistically significant when assessing the risk of melanoma metastasis. A previous study by de Vries et al. collected data from 10,538 patients diagnosed with melanoma from 1993 to 2004 in the Netherlands. The results of that study showed the primary site of melanoma and the mitotic rate are not statistically significant factors in melanoma distant metastasis (14). Ny et al. found that *BRAF* mutation is statistically significantly associated with reduced overall survival (HR [95% confidence interval (CI)]: 1.23 [1.09–1.38]) (20) and *BRAF* mutation in melanoma is most likely to occur prior to the development of metastatic disease (21). That some of these in this study were not found to be statistically significant may be due to the fact that this was a retrospective study and that only a few of the patients had been checked for *BRAF*.

LIMITATIONS

Our retrospective study collected data from medical records, resulting in instances of incomplete information regarding follow-up to ensure there had been sufficient time to accurately determine the incidence of melanoma metastasis. Additionally, the study was carried out at a single center, a tertiary care hospital in the north of Thailand, so the results may not be representative of the population of the entire country.

CONCLUSIONS

Factors associated with distant metastasis of cutaneous melanoma include Breslow thickness greater than 2 mm and metastasis into regional lymph nodes. Patients with these factors

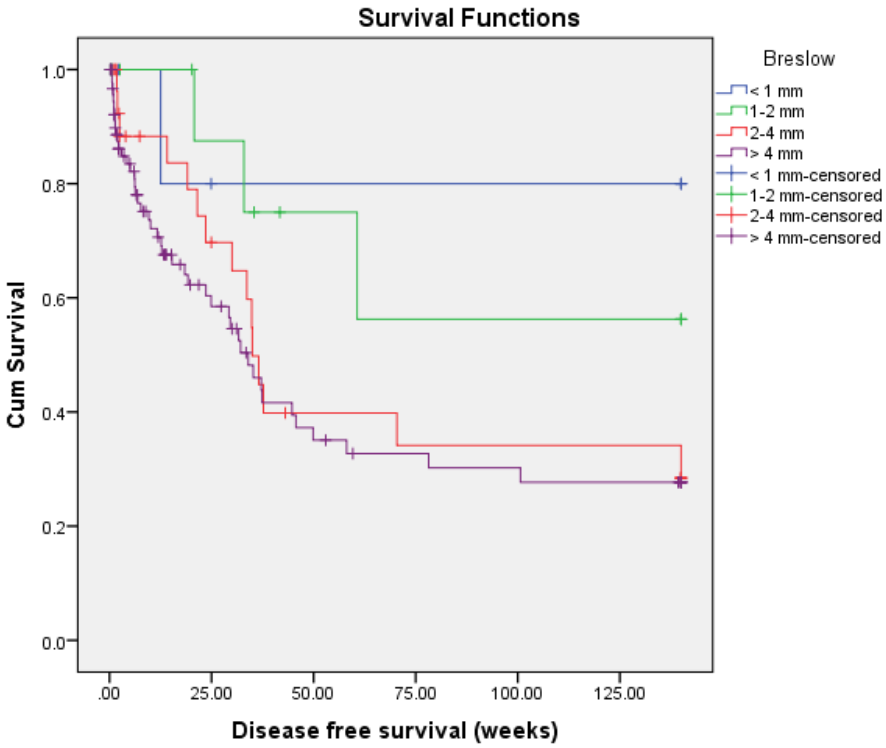

Figure 1. Kaplan-Meier curve showing the time interval for occurrence of metastasis in patients with cutaneous melanoma as a function of Breslow thickness

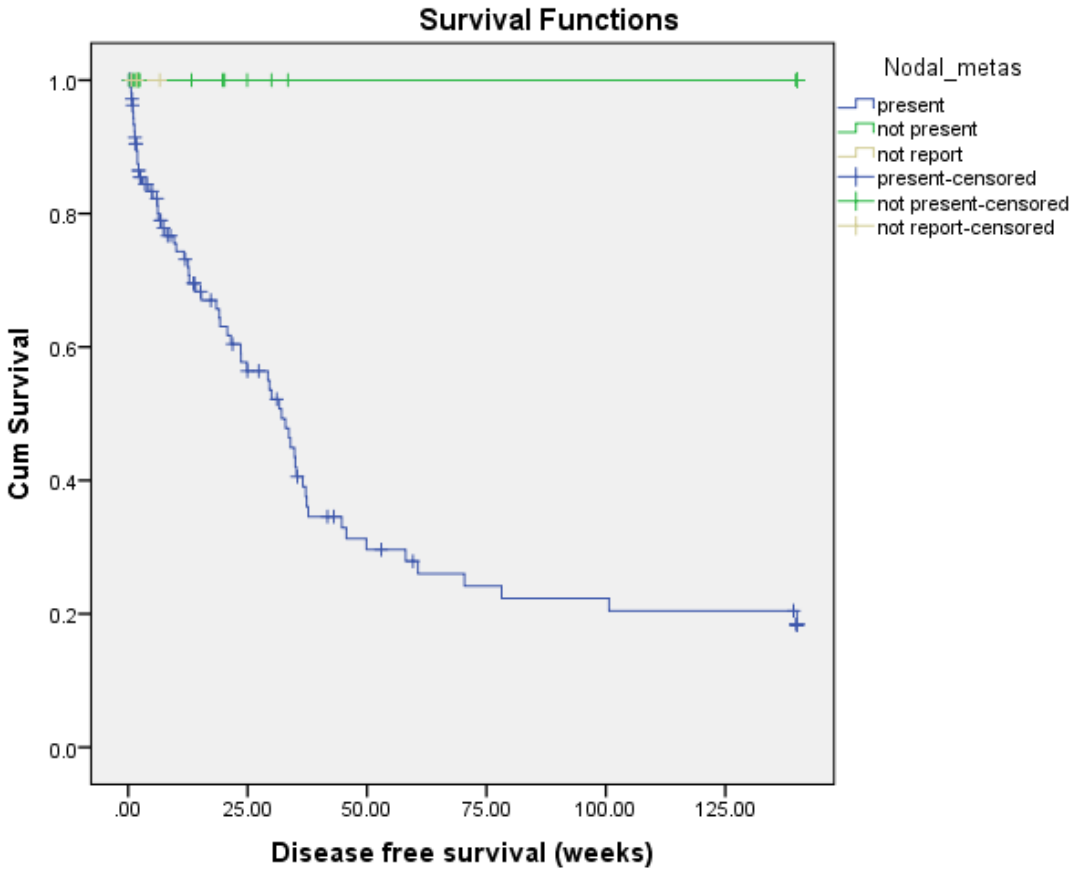

Figure 2. Kaplan-Meier curve showing the interval for occurrence of metastasis in patients with cutaneous melanoma according to lymph nodes metastasis

should be aggressively investigated for distant metastasis.

Disclosable non-financial conflicts of interest will also include membership or affiliation to nongovernmental organizations that have an interest in the submission and no significant financial support for this work that could have influences its outcome.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144:1941-53.
2. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol. 2009;20 Suppl 6(Suppl 6):vi1-7.
3. Cherobin ACFP, Wainstein AJA, Colosimo EA, Goulart EMA, Bittencourt FV. Prognostic factors for metastasis in cutaneous melanoma. An Bras Dermatol. 2018;93:19-26.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59: 225-49.
5. Balch CM, Soong SJ, Murad TM, Smith JW, Maddox WA, Durant JR. A multifactorial analysis of melanoma. IV. Prognostic factors in 200 melanoma patients with distant metastases (stage III). J Clin Oncol. 1983;1:126-34.
6. Neuman H, Patel A, Hanlon C, Brady M, Halpern A, Houghton A, et al. A single-institution validation of the AJCC staging system for stage IV melanoma. Ann Surg Oncol. 2007;25(18_suppl):8517.
7. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. Cancer J Clin. 2017;67:472-92.
8. Filippi AR, Fava P, Badellino S, Astrua C, Ricardi U, Quaglino P. Radiotherapy and immune checkpoints inhibitors for advanced melanoma. Radiother Oncol. 2016;120:1-12
9. Vatanasapt V, Martin N, Sriplung H, Chindavijak K, Sontipong S, Sriamporn H, et al. Cancer incidence in Thailand, 1988-1991. Cancer Epidemiol Biomarkers Prev. 1995;4:475-83.
10. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg. 1970;172:902-8.
11. Balch CM, Murad TM, Soong SJ, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg. 1978;188:732-42.
12. Brauer JA, Wriston CC, Troxel AB, Elenitsas R, Shin DB, Guerry D, et al. Characteristics associated with early and late melanoma metastases. Cancer. 2010;116:415-23.
13. Pollack LA, Li J, Berkowitz Z, Weir HK, Wu XC, Ajani UA, et al. Melanoma survival in the United States, 1992 to 2005. J Am Acad Dermatol. 2011;65(5 Suppl 1):S78-86
14. de Vries E, Nijsten TE, Visser O, Bastiaannet E, van Hattem S, Janssen-Heijnen ML, et al. Superior survival of females among 10 538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. Ann Oncol. 2008;19:583-9.
15. Mervic L. Time course and pattern of metastasis of cutaneous melanoma differ between men and women. PLoS One. 2012;7:e32955.
16. Denat L, Kadekaro AL, Marrot L, Leachman SA, Abdel-Malek ZA. Melanocytes as instigators and victims of oxidative stress. J Invest Dermatol. 2014; 134:1512-18.
17. Conley J, Lattes R, Orr W, Surgery R. Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer. 1971;28:914-36.
18. Rutkowski P, Nowecki ZI, Zdzienicki M, Michej W, Symonides M, Rosinska M, et al. Cutaneous melanoma with nodal metastases in elderly people. Int J Dermatol. 2010;49:907-13.
19. Balch CM, Wilkerson JA, Murad TM, Soong SJ, Ingalls AL, Maddox WA. The prognostic significance of ulceration of cutaneous melanoma. Cancer. 1980; 45:3012-7.
20. Ny L, Hernberg M, Nyakas M, Koivunen J, Oddershede L, Yoon M, et al. *BRAF* mutational status as a prognostic marker for survival in malignant melanoma: a systematic review and meta-analysis. Acta Oncol. 2020;59:833-44.
21. Libra M, Malaponte G, Navolanic PM, Gangemi P, Bevelacqua V, Proietti L, et al. Analysis of *BRAF* mutation in primary and metastatic melanoma. Cell Cycle. 2005;4:1382-4.

Appendix. The mean time interval from diagnosis of first-ever melanoma to distant metastasis

Variable	Time (weeks)
Gender	
Male	58.66
Female	70.10
Site	
Head and neck	41.41
Trunk	65.75
Upper limbs	73.52
Lower limbs	68.56
Acral	65.10
Superficial spreading	79.34
Nodular	60.83
Clinicopathological subtype	
Acrolentigenous	54.39
Lentigo maligna	80.36
Desmoplastic	15.88
Clark level	
I	12.56
II	103.46
III	82.47
IV	67.56
V	49.78
Breslow thickness	
< 1 mm	114.51
1 - 2 mm	96.83
2 - 4 mm	66.03
> 4 mm	56.83
Ulceration	
Present	45.54
Not present	99.12
Mitotic index	
0	50.83
1 - 4	46.76
5 - 10	37.19
≥ 11	43.50
Lymphocyte infiltrate	
Present	100.50
Not present	62.76
BRAF 600	
Positive	45.53
Negative	51.23
Nodal metastasis	
Present	30.79
Not present	68.02

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Original Article **Open Access**

Treatment Outcomes of Transcatheter Closure in Common Congenital Heart Disease: Success Rate and Short-term Complications

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ABSTRACT

OBJECTIVE This study aimed to investigate treatment outcomes, including success rates and any short-term complications of transcatheter closure in common congenital heart disease (CHD), ventricular septal defect (VSD), atrial septal defect (ASD) and patent ductus arteriosus (PDA) at our tertiary cardiac center.

METHODS This retrospective study was conducted at Naresuan University Hospital, Thailand. We enrolled patients for the analysis who had undergone transcatheter device closure (VSD, ASD and PDA) from October 2011 through May 2018. Treatment outcome success is defined as complete closure at 1 day, 1 month and 6 months following the procedure. Major complications associated with transcatheter device closure such as device embolization, arrhythmia, cardiac tamponade, thromboembolism, cardiac erosion and death were also collected.

RESULTS Ninety-four patients, ranging from children to adults, were enrolled. ASD, PDA and VSD device closure was done in 45, 40 and 9 patients, respectively. Overall success at 1 day, 1 month and 6 months following the procedure were 87.3, 92.1 and 96.8%, respectively. There were 2 complications reported, one thromboembolism and one first-degree atrioventricular block (AVB).

CONCLUSIONS Transcatheter closure in common congenital heart diseases provides good treatment outcomes and is safe for all age groups, from children to adults, with only a small number of major complications.

KEYWORDS congenital heart disease, transcatheter closure, treatment outcome, ASD device closure, VSD device closure, PDA device closure

INTRODUCTION

Congenital heart disease (CHD) is a common birth defect which varies in complexity from a simple single to a fatal complex CHD lesion. The prevalence is 9.4:1,000 live births. The three most common types of CHD are ventricular septal defect (VSD), atrial septal defect (ASD) and patent ductus arteriosus (PDA) (1). Standard treatment guidelines for these defects, either surgical or transcatheter closure, have been published for several decades (2). Transcatheter device closure was introduced several years ago as a treatment for PDA (3), followed by ASD (4) and VSD (5). Outcomes of transcatheter device closure in previous studies have been reported to be more favorable, to result in faster recovery and to be less invasive than surgical treatment, especially ASD and VSD which require open-heart surgery techniques (6,7). Although several studies have reported excellent success rates with defect closure using the transcatheter technique, there are some limitations as the device may not be suitable for all patients due to anatomical variation and a defect size not appropriate to currently available devices (6-11). Transcatheter device closure

complications include device embolization, arrhythmias or conduction problems, cardiac tamponade, thromboembolism, stroke and death. There are some specific complications for related to each procedure, e.g., device erosion which has been found in ASD devices (6), coarctation of the aorta after PDA device closure (9, 10) and complete atrioventricular block after VSD device closure (11). This study aimed to investigate treatment outcomes, including success rates and any short-term complications, of transcatheter closure in common CHD (VSD, ASD and PDA) at our tertiary cardiac center.

METHODS

This retrospective analysis was conducted at Naresuan University Hospital, Thailand. We enrolled patients diagnosed with VSD, ASD and PDA who had undergone transcatheter device closure between October 2011 and May 2018. Patients' demographic data (age, sex) was collected by hospital medical record review. The diagnosis of congenital heart disease for each patient and the decision regarding device size selection were made by a cardiologist using standard echocardiography. Catheterization reports, including procedure time, fluoroscopic time and evidence of pulmonary hypertension, were also collected. Treatment outcomes, including success rate and any complications, were evaluated. Success, defined as "complete closure" reflected with no residual lesion observed on echocardiography, was evaluated by a cardiologist at 1 day, 1 month and 6 months after device closure. Major complications associated with transcatheter device closure, including device embolization, arrhythmia, cardiac tamponade, thromboembolism, cardiac erosion and death, were collected.

Patients who underwent transcatheter closure for any defect and who were reported as complete closure at post-procedure day 1 were defined as "immediately successful closure". The relative proportion of the size of device used and the size of the defect was calculated as a percentage and compared between patients with immediate successful closures and those with residual lesions. In this study, a Cocoon® device (Vascular Innovations Co., Ltd., Nonthaburi, Thailand) was chosen based on cost effectiveness compared to the other brands with no conflict of interest involved. All procedures performed involving human participants were conducted in accordance with the ethical standards of the Naresuan University Institutional Review Board (NU-IRB) and the 1964 Helsinki Declaration as amended or comparable ethical standards. Informed consent was obtained from all participants involved in the study.

Statistical analysis

Continuous data are presented as mean and standard deviation or median and maximum with minimum for data distribution. Categorical data are shown as frequency and percentage.

RESULTS

A total of 135 patients diagnosed with correctable cardiac lesion who underwent transcatheter device closure from October 2011 through May 2018 at Naresuan University Hospital were eligible for the study. Among those patients, three were referred for surgery including one child with ASD with absence of posterior rim on transesophageal echocardiography (TEE), one adult with a large, distended ASD of 34 mm in diameter which was too large for any device. The third patient referred for surgery was a child diagnosed with PDA with significant coarctation of the aorta identified by aortogram under fluoroscopy with a pressure gradient of 25 mmHg. Patients with incomplete data or who were lost to follow-up were also excluded. A total of 94 patients who had a complete transcatheter closure procedure were enrolled in the study. ASD device closure was done in 45 patients; PDA device and VSD device closure was done in 40 and 9 patients, respectively (Figure 1). The types of ASD and PDA devices were Cocoon septal and duct Occluder. The VSD devices included 5 Cocoon VSD Aneurysm and 4 Cocoon VSD Membranous and Muscular devices. Patients' age distribution was 0-17 years (67%), 18-49 years (14.9%) and in 50 years and above (18.1%). Among the patients aged 0-17 years, PDA device closure was the most common procedure, whereas an ASD device was most frequently used in patients aged 18-49 years and aged 50 years and above. Pulmonary

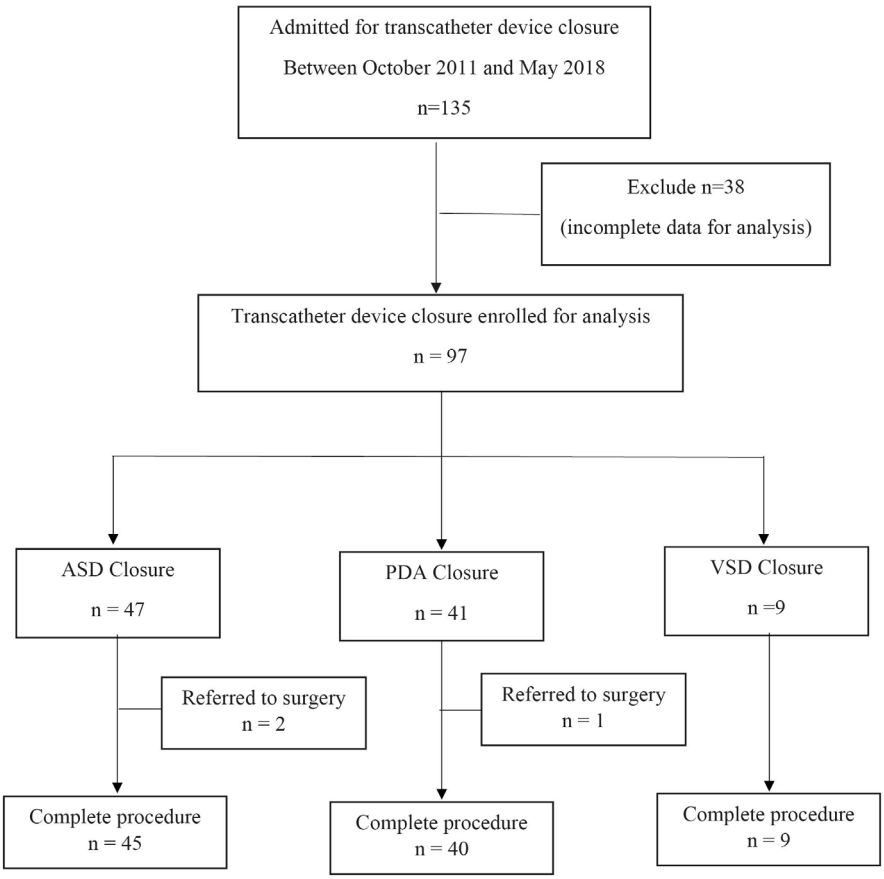

Figure 1. Consort diagram. Characteristics of study participants
ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus

hypertension was reported in half the patients with ASD devices (46.7%). The mean procedure time with ASD devices was 65.8 (±32.1) minutes and the median fluoroscopy time was 7 minutes (range 2.3 to 46.3 minutes). For PDA devices, the mean procedure time was 71.1 (±25.5) minutes and the median fluoroscopy time was 11.5 minutes (range 0.7 to 80.2 minutes). For VSD devices, the mean procedure time was 107.9 (±36.5) minutes and for fluoroscopy time was 21.5 minutes (range 9.2 to 62.3 minutes) (Table 1).

Success rate and complications

The overall success rate at 1 day, 1 month and 6 months for all transcatheter closures were 87.3, 92.1 and 96.8%, respectively. For ASD devices, the success rate at 1 day, 1 month and 6 months were 91.1, 93.3 and 95.5%, respectively. PDA device success rates at 1 day, 1 month and 6 months were 82.5, 95 and 97.5%, respectively. VSD devices success rates at 1 day, 1 month and 6 months were 77.8, 77.8 and 100%, respectively. Only two patients experienced complications after the procedure. One patient, aged 49, reported thromboembolism which manifested as stroke with symptoms of dysarthria without any weakness immediately after ASD device closure. The second patient, aged 11, had a first-degree atrioventricular block (AVB) at the 6-month follow up for ASD device closure. There were no reports of device embolization, cardiac erosion, complete atrioventricular block or death (Table 2).

Among patients with immediately successful closure, the mean device to defect size proportions ratio, expressed as percent, were 117.8% for ASD, 170.2% for PDA and 111.6% for VSD devices. The proportion ratio of the size of the device to the size of the defect was slightly larger among the immediately successful closure group than those with residual lesions (Table 3).

DISCUSSION

Transcatheter closure in common CHD has been used for several decades because of

Table 1. Patient characteristics

	All (n=94)	ASD (n=45)	PDA (n=40)	VSD (n=9)
Age (%)				
0-17 years	63 (67.0)	19 (42.2)	36 (90.0)	8 (88.9)
18-49 years	14 (14.9)	10 (22.2)	3 (7.5)	1 (11.1)
≥ 50 years	17 (18.1)	16 (35.6)	1 (2.5)	0
Female (%)	63 (67)	30 (66.7)	31 (77.5)	2 (22.2)
Procedure time (minutes) mean (±SD)	72.1 (±31.9)	65.8 (±32.1)	71.1 (±25.5)	107.9 (±36.5)
Fluro time (minutes)	10.1	7	11.5	21.5
median (max:min)	(0.7 : 80.2)	(2.3 : 46.3)	(0.7 : 80.2)	(9.2 : 62.3)
Pulmonary hypertension (%)	31 (32.9)	21 (46.7)	7 (17.5)	3 (33.3)

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus

Table 2. Treatment outcomes: success rates and complications

After procedure	All (%)	ASD (%)	PDA (%)	VSD (%)
1 day	82 (87.3)	41 (91.1)	33 (82.5)	7 (77.8)
1 month	87 (92.1)	42 (93.3)	38 (95.0)	7 (77.8)
6 months	91 (96.8)	43 (95.5)	39 (97.5)	9 (100)
Complications				
Thromboembolism	1	1	-	-
Atrioventricular block	1	1	-	-
Device embolization	-	-	-	-
Cardiac erosion	-	-	-	-
Death	-	-	-	-

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus

Table 3. Mean device to lesion size (percent) and immediate treatment outcome (after 1 day)

Treatment outcome	Device: lesion size (%)		
	ASD	PDA	VSD
Complete closure	117.8 (n=41)	170.2 (n=33)	111.6 (n=8)
Incomplete closure	115.9 (n=4)	164.9 (n=7)	85.7 (n=1)

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus

its efficiency and because it is less invasive compared to surgical techniques. Especially in younger children, infants or patients with underlying conditions, the transcatheter technique has been shown to be more beneficial than referring patients for an operation (6, 7, 12). Our study found good outcomes with few reported complications with the transcatheter technique for closing any common defect in all age groups which is in accord with previous studies (6-10).

Only two major complications were reported at the 6-month follow-up, one AVB and one ischemic stroke. Rhythm disturbance is a rare complication following ASD device closure. There have been some reports of first or third-degree AVB following the procedure which were treated surgically by device removal and with corticosteroids (13-15). The mechanism of this rhythm disturbance may be any direct trauma to the conduction system, e.g., an intraoperative finding in an ASD device removal operation showed right atrium disk compression at the triangle of Koch with a small hematoma (13), or any inflammation. However, from the previous reports VSD devices were found to be more complicated frequently associated with AVB, especially perimembranous type VSD according due to the anatomical location close to the bundle of His, than any other type of device. Our study found only one case of hemodynamically stable, first-degree AVB following ASD device closure. A recent study of 70 Saudi Arabian children who underwent VSD device

closure found 2.9% of the cases experienced transient conduction abnormalities (bradycardia, asystole or complete AVB), while another 2.9% had complete AVB following the procedure that required a permanent pacemaker or surgical intervention (16). A recent meta-analysis, however, found no significant difference in the incidence of complete AVB between the transcatheter and surgical closure techniques (12). Our study did not find any complications among patients with VSD devices, although this may be due to the limited number of cases.

Thromboembolism is a common complication in both diagnostic and interventional cardiac catheterization. A previous study in New York reported an incidence of 0.18% for stroke events following coronary angiography. Our study reported one case of an ischemic stroke event following ASD device closure. Heparinization, frequent catheter aspiration and flushing are standard guidelines for prevention of thromboembolism events during the procedure (17).

Another interesting complication is atrial wall erosion after ASD device closure. A recent case series found that 88% of patients with atrial wall erosion had an aortic rim deficiency.

The United States Food and Drug Administration Panel Review has labeled a retro-aortic rim that is lesser than 5 mm in diameter as a relative contraindication for ASD device closure (19). Although our study did not report any atrial wall erosion events during the 6-month follow-up period, we continuously monitor for this event.

Comparison of the ratio of the size of the device used and the size of the defect showed that patients with immediately successful closure had received larger devices compared to those with residual lesions. This may help in provides provisional guidance for choosing the proper size of device for each patient by considering the individual defect size; however, due to the limited number of patients in this study, additional investigation is needed to establish conclusive guidelines.

CONCLUSIONS

Transcatheter closure in common congenital heart diseases results in successful and safe treatment outcomes in all age groups, from children to adults with only a small number of major complications. A larger device size relative to the size of the lesion may result in immediate complete closure. However, currently available devices may not suitable for all patients due to anatomical variations and large defect sizes relative to the size of the devices.

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CONFLICTS OF INTEREST STATEMENT

The authors have each completed the International Committee of Medical Journal Editors Form for uniform disclosure of potential conflicts of interest. No authors have any potential conflict of interest to disclose.

REFERENCES

1. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019;48:455-63.
2. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021;42:563-645.
3. Porstmann W, Wierny L, Warnke H. Closure of persistent ductus arteriosus without thoracotomy. Ger Med Mon. 1967;12:259-61.
4. King TD, Thompson SL, Steiner C, Mills NL. Secundum atrial septal defect. Nonoperative closure during cardiac catheterization. JAMA. 1976;235:2506-9.
5. Lock JE, Block PC, McKay RG, Baim DS, Keane JF. Transcatheter closure of ventricular septal defects. Circulation. 1988;78:361-8.
6. O'Byrne ML, Levi DS. State-of-the-art atrial septal defect closure devices for Congenital heart. Interv Cardiol Clin. 2019;8:11-21.
7. Liu S, Chen F, Ding X, Zhao Z, Ke W, Yan Y, et al. Comparison of results and economic analysis of surgical and transcatheter closure of perimembranous ventricular septal defect. Eur J Cardiothorac Surg. 2012;42:e157-62.
8. Faccini A, Butera G. Atrial septal defect (ASD) device trans-catheter closure: limitations. J Thorac Dis. 2018;10:S2923-30.
9. Baruteau AE, Hascoët S, Baruteau J, Boudjemline Y, Lambert V, Angel CY, et al. Transcatheter clo-

sure of patent ductus arteriosus: past, present and future. Arch Cardiovasc Dis. 2014;107:122-32.
10. P S, Jose J, George OK. Contemporary outcomes of percutaneous closure of patent ductus arteriosus in adolescents and adults. Indian Heart J. 2018;70:308-15.
11. Morray BH. Ventricular septal defect closure devices, techniques, and outcomes. Interv Cardiol Clin. 2019;8:1-10.
12. Saurav A, Kaushik M, Mahesh Alla V, White MD, Satpathy R, Lanspa T, et al. Comparison of percutaneous device closure versus surgical closure of perimembranous ventricular septal defects: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2015;86:1048-56.
13. Sato J, Kato A, Takeda S, Nishikawa H. Case report: atrioventricular block after transcatheter atrial septal closure using the Figulla® Flex II ASD occluder. Catheter Cardiovasc Interv. 2019;93:E298-301.
14. Chantepie A, Lefort B, Soulé N, Bonnefoy R, Labarthe F. Atrioventricular block after transcatheter atrial septal defect closure using the Amplatzer septal occluder(®). Arch Pediatr. 2013;20:1333-6.
15. Al-Anani SJ, Weber H, Hijazi ZM. Atrioventricular block after transcatheter ASD closure using the Amplatzer septal occluder: risk factors and recommendations. Catheter Cardiovasc Interv. 2010; 75:767-72.
16. Khoshhal SQ, Al-Mutairi MB, Alnajjar AA, Morsy MM, Salem SS, Al-Muhaya M, et al. Transcatheter device closure of ventricular septal defects in children: a retrospective study at a single cardiac center. Ann Saudi Med. 2020;40:396-402.
17. Wong SC, Minutello R, Hong MK. Neurological complications following percutaneous coronary interventions (a report from the 2000-2001 New York State Angioplasty Registry). Am J Cardiol. 2005;96:1248-50.
18. Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. Catheter Cardiovasc Interv. 2004;63:496-502.
19. Mallula K, Amin Z. Recent changes in instructions for use for the Amplatzer atrial septal defect occluder: How to incorporate these changes while using transesophageal echocardiography or intracardiac echocardiography. Pediatr Cardiol. 2012; 33:995-1000.

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Development of Thai Spondee Words for SRT Measurement in Children

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ABSTRACT

OBJECTIVE The purpose of this study was to develop standardized Thai speech material for use in the measurement of speech recognition threshold (SRT) in children.

METHODS The Thai speech material was developed according to three essential criteria: children's familiarity with the word, phonetic dissimilarity, and homogeneity with respect to basic audibility. Disyllabic words selected from a Thai fundamental word list used in teaching the Thai language at the primary level were analyzed to measure the intensity of each syllable using a Computerized Speech Lab (CSL). The spondee words were then assessed for familiarity by the parents or guardians of the children. A total of 60 spondee words were selected for use in evaluating the threshold of recognition of each word by 30 normal-hearing children.

RESULTS Of the 60 spondee words, 25 words with relatively steep and homogeneous psychometric function slopes were selected for inclusion in a list of Thai speech material for children. The psychometric function slopes at the 50% threshold of the final 25 spondee words were found to have a mean of 10.76 %/dB.

CONCLUSIONS The Thai speech material for children was developed according to the speech material criteria. This list of words is suitable for use in evaluating the SRT of normal-hearing children

KEYWORDS SRT, speech recognition materials, Thai spondee words

INTRODUCTION

Hearing is considered to be one of the most crucial of the five human senses and is essential to the process of speech and oral language development. In order to evaluate the hearing ability of children, a complete set of audiological tests is required. The standard audiological test battery consists of measurements of pure-tone air conduction, pure-tone bone conduction, speech recognition threshold (SRT), and word recognition score (WRS).

The Speech Recognition Threshold (SRT), part of the test battery used in speech audiometry, is the minimum hearing level at which an individual can perceive 50 percent of recognized speech material (1). SRT is commonly determined by asking the person to repeat spondee words, disyllabic words with equal stress on each syllable. For SRT material, there are three essential criteria that should be met: familiarity, phonetic dissimilarity, and homogeneity with respect to basic audibility (2).

Thai is the official language for both speaking and writing in Thailand. The syllables of Thai words are comprised of consonants, vowels, and tones (3). There are five tones in Thai: mid, low, falling, high, and rising (4), with different tone pronunciations corresponding to different

meanings. In contrast, in English, a non-tonal language, in some cases differentiation between the meanings of words is indicated by the degree of stress emphasis. Thai spondee words are disyllabic words with equal loudness and with a difference of no more than ±2 dB on each syllable (5).

There are only two sets of Thai materials for SRT measurement that are currently being used in Thailand. The first is RAMA SRT-1, developed in 1973 (6), which uses spondee words for SRT measurement. At that time, the homogeneity of audibility did not meet the criteria because of limitations of available acoustic instruments. A second set of Thai material, RAMA SRT-2 (7), was developed in 1980 which better meet the criteria of SRT materials. However, neither of these was developed specifically for use in hearing evaluation of children.

Children regularly react to speech stimuli because speech is a signal of interest to most young children. Audiologists can estimate a child's ability to hear and understand by observing their responses (8). One of the simplest tests of speech is SRT. An SRT measurement can be made for children from about three to four years and up to eight years of age (9) by the use of an appropriate children's word list.

Due to the lack of a standard children's speech material list in Thai, pediatric audiologists have had to use adult materials in evaluating the hearing of young children. Differences in thresholds can be clinically significant when adult materials are used with children (10). The problem is exacerbated by a reduction in the set size (11) because of the children's unfamiliarity with some of the test items. To avoid an erroneous estimation of a child's recognition skills, word lists and set size should not be simply reduced (12). Rather, stimulus lists with the appropriate properties need to be developed. The purpose of the present study was to develop Thai speech material to be used for speech recognition threshold (SRT) measurement of Thai children with normal hearing age 4 to 8 years.

METHODS

Ethical approval for the present study was obtained from the Ethical Clearance Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (ID 08-61-14).

Speech material

1. All of the words must be spondee words in which each syllable is equal in loudness and is familiar to children. Therefore, the materials should be generally used in their everyday life and be well-known by children.
2. All of the words in the list ought to be different in phonetics so that an auditory cue will not be given to the child. For example, in cases of two words with the same pronunciation in one of the syllables, e.g., rot-fai (train) and rot-yon (car), only one word is allowed.
3. All of the spondee words should be homogeneous in audibility, i.e., each word in the test list should tend to reach the threshold of speech at the same presentation level. Thus, the word intelligibility will be within a narrow range of intensity, and its psychometric function will rise steeply from zero to one hundred percent.

Following these three criteria, the material was developed in three steps:

1. *Spondee words test*

All mono-and disyllabic words were collected from a 'List of Thai Fundamental Words' published by the Thai Ministry of Education (13). According to a study conducted in 2008, the list is still used in Thai language schoolbooks (14). This study identified the words that were most frequently spoken by children from all regions of Thailand. In the list of fundamental words for kindergarten and first grade children, there were 140 disyllabic words and 171 monosyllabic words. All of the 171 monosyllabic words were nouns, pronouns, verbs or conjunctions. Monosyllabic words were combined into 220 disyllabic words after meaningless words were removed. The result was a total of 360 disyllabic words which had been tested for the characteristics of spondee words.

A spondee word is a disyllabic word with equal loudness, which has a difference between each syllable of about ±2 decibel (dB) on a volume unit (VU) meter (5). To test the spondee characteristics of disyllabic words, a 4500 model Computerized Speech Lab (CSL) was used. The CSL could compute the energy of a range of speech waveform data and display the energy

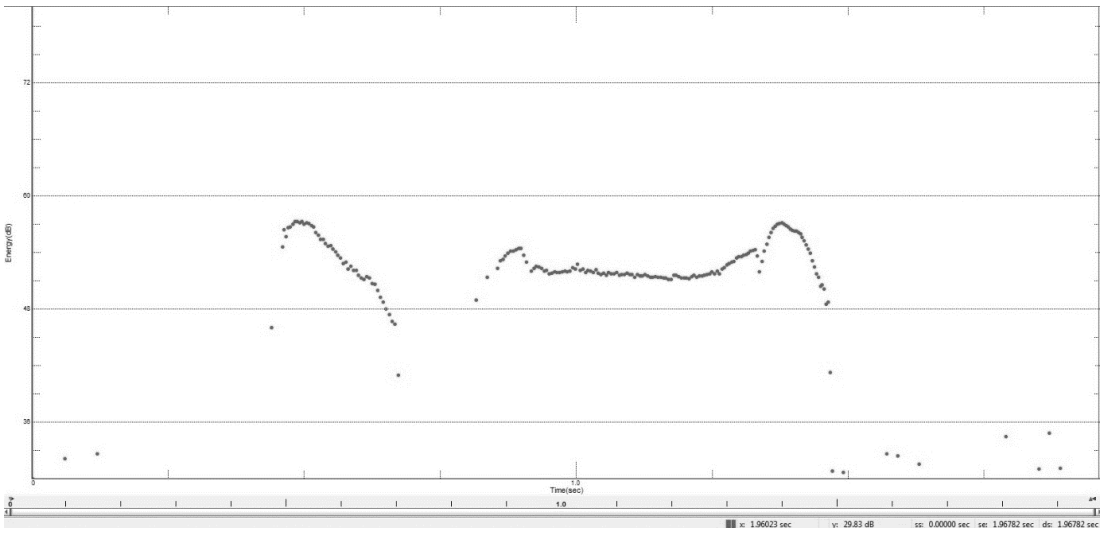

Figure 1. The energy contours (dB SPL) during the time (sec) of the disyllabic word "อาบน้ำ" (ʔàːp nám). The first and second syllables were approximately equal in loudness, so it was considered a spondee word.

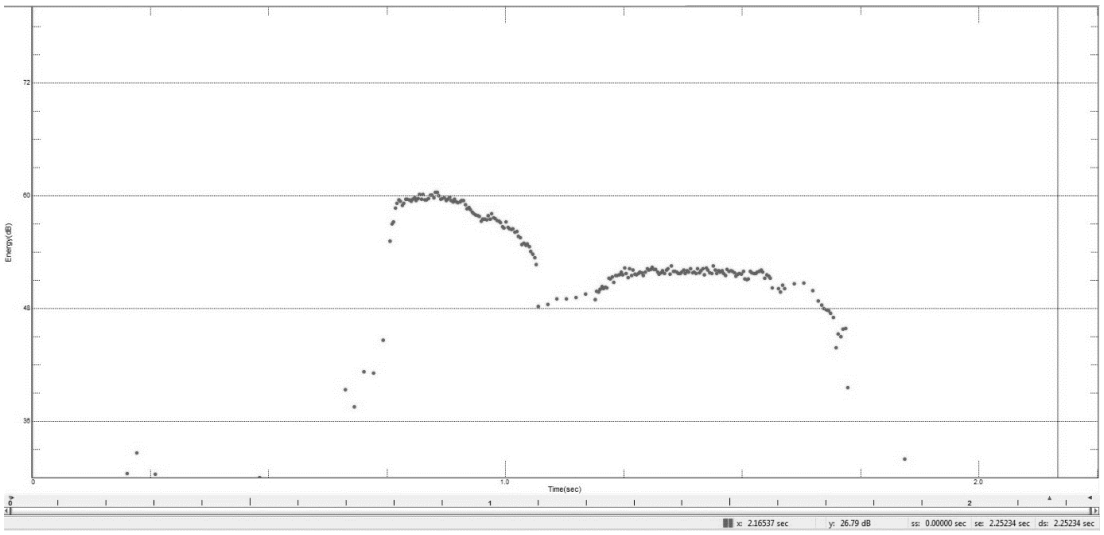

Figure 2. The energy contour (dB SPL) during the time (sec) of the disyllabic word "พ่อแม่" (pʰɔ̂ː mɛ̀ː). The first and second syllables were not equal in loudness. Consequently, "พ่อแม่" (pʰɔ̂ː mɛ̀ː) was not considered to be a spondee word.

contour results as a decibel sound pressure level (dB SPL). After all the disyllabic words had been analyzed with CSL, 140 spondee words which meet the criteria were chosen. Figures 1 and 2 show the energy contours of the first and second syllables of disyllabic words from CSL.

2. *Familiarity words test*

Twenty Thai native speakers who were parents or guardians of a 4- to 8-year-old child rated the familiarity of 140 spondee words on a scale of 1 to 5 based on the familiarity of each word according to his/her child (5 = extremely familiar, 4 = very familiar, 3 = somewhat familiar, 2 = slightly familiar, and 1 = unfamiliar). After calculating the mean score of each spondee word, the words with a mean rating score of < 4 and those having the same pronunciation with different meanings were eliminated. As a result, 60 spondee words were retained for further use.

To habituate a child before administering the recognition-of-word test, a word familiarization list was created. Five experienced pediatric audiologists with over three years professional experience rated frequently used words in a child speech hearing evaluation. There are a total of 109 Thai spondee words in RAMA. SRT-1 and in RAMA. SRT-2 which were developed for

SRT measurement of adults. All of the adult spondee words were rated on a scale of 1 to 5 based on the frequency of use in children's SRT measurements (5 = always used, 4 = usually used, 3 = often used, 2 = rarely used, and 1 = never used). After calculating the mean score of each spondee word, the words with a mean rating score higher than 3 were included in the word familiarization list. There were 20 words that had a mean rating score higher than 3, but seven were the same as developed words and so were excluded. Finally, there were 13 words for habituation of the child.

3. Recordings

In order to ensure the perception equality of the word lists, a master recording of the words was created based on the noise criteria class 30 in a recording studio using a Studio Six filter-based one-third octave real time analyzer with iTestmic2, type 2-class measurement microphone. A large diaphragm condenser microphone (Audio-Technica model 4050) was positioned 20 cm from the speaker at 0° azimuth with a double-cloth type mesh filter in between. The audio signal was transferred to a Beringer XR18 analog-to-digital converter for digitization.

A female audiologist used normal vocal effort in the pronunciation of each spondee word at least three times. The records that had the best quality based on vocal quality, uninterrupted speech sound, equality of effort in each syllable, absence of background noise, and that the listener could hear clearly were selected by the audiologist for the recognition evaluation part of the study. After the selection process, each of the spondee words was normalized as a single utterance at the same level equivalent to that of a 1 kilohertz (kHz) calibration tone, and then converted to 16-bit/44.1 kHz as the final step in the mastering process.

Participants

A group of 30 healthy native speaking Thai children (16 girls and 14 boys) with an age range of 4;0 to 7;11 (years; months) (mean 5.74 ± 1.8) were recruited for this study and were accompanied by a parent/guardian to Ramathibodi Hospital. Each participant passed the following screening: 1) Normal outer and middle ear verified by otoscopy and tympanometry demonstrating no cerumen impaction and a type A tympanogram, 2) Normal hearing sensitivities at 250, 500, 1000, 2000, and 4000 Hz (≤ 25 dB HL) indicated by a pulsed tone audiogram, 3) Normal speech and language development as evaluated by case history questionnaires (adapted from the Developmental Surveillance and Promotion Manual (15)) for speech, language, hearing, and medical histories completed by the parent/guardian of each participant. Every child was currently studying in a regular school and had passing grades. In addition, the parent/guardian of the child signed the consent form for children who were less than 7 years of age. Children 7 years and older signed the consent form themselves. The mean pulsed tone average (PTA) (arithmetic average of hearing thresholds at 500, 1000, 2000 Hz.) for the 30 children was 14.72 decibels Hearing Level (dB HL).

Procedures

The developed speech material lists were tested to insure that they met the homogeneity of audibility criteria. The 60 spondee words were divided into three lists, and there were 10 participants for each list. The signals of speech material were transferred from an iPad to the external input of an audiometer. The signal was then transferred by means of insert earphones from the audiometer to the participant who was seated in an audiometric exam booth accompanied by a research assistant. The inputs to the audiometer were calibrated to 0 VU using 1 kHz calibration prior to the test of each participant. Instructions regarding the SRT test were given to the child after hearing screening had been completed. Then, the familiarization word list was presented at 50 dB HL. If the child repeated five words correctly, the developed speech materials were then played.

Each of the developed spondee words was initially presented to the child at a sound level 10 dB below the child's PTA. The child repeated each word verbally and their response was scored as correct or incorrect. If the child repeated the word incorrectly, the intensity was increased in 2 dB increments until the child repeated it correctly or until the maximum intensity at 26 dB HL was reached (above the

normal limit). If the child still repeated a word incorrectly, the next word would be presented. In addition, positive reinforcement, e.g., compliments, stickers, or toys, were given to the child during the test as a reward and to increase their motivation.

Data analysis

Logistic regression was used to determine the regression slope and intercept for each of the spondee words. These values were then used in modified logistic regression equations designed to calculate the percentage of correct recognition at each intensity level. Each of the 60 spondee words was analyzed using logistic regression to compute their regression slopes and intercepts using the following four equations.

$$ln\frac{p}{1-p} = a + bi \quad (1)$$

In equation 1, p is the proportion of correct recognition at any intensity level, a is the regression intercept, b is the regression slope, and i is the intensity level in dB HL. When Equation 1 is solved for p and multiplied by 100, Equation 2 is obtained:

$$P = \left(\frac{\exp(a+bi)}{1+\exp(a+bi)}\right)\times 100 \quad (2)$$

In equation 2, the percentage of correct recognition at any intensity level can be computed. The percentage of correct recognition was calculated for each of the spondee words over a range of -10 to 26 dB HL in 2 dB increments.

In order to calculate the intensity level required for a given proportion, equation 1 was solved for i (equation 3). The threshold (intensity required for 50% intelligibility) and the slope (%/dB) at threshold can be computed when the desired proportions are used in equation 3. Equation 3 can be simplified to equation 4 to solve for the threshold (p = 0.5).

$$i = \frac{ln\frac{p}{1-p} - a}{b} \quad (3)$$

$$i = \frac{-a}{b} \quad (4)$$

Calculations of the threshold intensity (intensity required for 50% intelligibility) and a slope of 50% were made for each spondee word using the logistic regression slopes and intercepts.

RESULTS

The mean threshold of 50% recognition for the 60 spondee words was 25.14 dB HL (standard deviation (SD) = 3.17). The minimum and maximum thresholds were 18.85 and 33.71 dB HL, respectively. Equation 2 was used to calculate the psychometric functions for each spondee word. The mean psychometric function slope at 50% was 9.60 %/dB (SD = 3.50) and ranged from 4.10 %/dB to 18.75 %/dB.

The final criteria in development of the speech material for SRT measurement was homogeneity of audibility. To meet the standard criteria, the spondee words with the steepest psychometric function slope were selected. There were 25 spondee words in the final list of Thai spondee words for children. Mean of the psychometric function slope at 50% threshold was 10.76 %/dB (SD = 3.72) and ranged from 5.30 %/dB to 18.75 %/dB. Table 1 shows the logistic regression analysis data of the selected 25 spondee words for children including the thresholds, International Phonetic Alphabet spelling, meaning of each word, regression intercept, regression slope, and psychometric function slope at 50%. Figure 3 shows the psychometric functions for each of the 25 final spondee words and the data points. Figure 4 shows the psychometric function slopes for the final 25 spondee words for children.

DISCUSSION

The psychometric function slopes at the 50% threshold of the 25 spondee words for children developed for the present study were found to have a mean of 10.76 %/dB. This value is similar to those reported for other languages. The mean psychometric function slope at 50% for materials in English have generally been reported to be between 7.2 %/dB and 12.0 %/dB (2, 5, 16-18). The mean psychometric function slope at 50% for materials in recorded Taiwanese Mandarin has been reported to be 11.3 %/dB for male speakers and 11.7 %/dB for female speakers (19). In Japanese, the mean slope at 50% for materials developed in SRT measurement had

Table 1. Logistics analysis of results for the final 25 spondee words

	Spondee word	IPA	Meaning	RI[a]	RS[b]	Slope at 50%[c]	Thres.[d]	ΔM dB[e]
1	แปรง ฟัน	**prɛ:ŋ fan**	brush teeth	-8.445	0.448	11.20	18.85	4.13
2	ท้อง ฟ้า	**tʰɔ́:ŋ fá:**	sky	-5.445	0.277	6.93	19.66	4.94
3	ของ เล่น	**kʰɔ̌:ŋ lên**	toy	-6.981	0.352	8.80	19.83	5.11
4	อาบ น้ำ	**ʔà:p ná:m**	bathe	-7.507	0.372	9.30	20.18	5.46
5	บน โต๊ะ	**bon tóʔ**	on table	-7.412	0.359	8.98	20.65	5.93
6	ขวด นม	**kʰù:at nom**	milk bottle	-6.734	0.317	7.93	21.24	6.52
7	ทำ งาน	**tʰam ŋa:n**	work	-7.752	0.360	9.00	21.53	6.81
8	ผู้ชาย	**pʰû: tɕʰa:j**	man	-8.342	0.384	9.60	21.72	7.00
9	ลม พัด	**lom pʰát**	wind blows	-7.883	0.362	9.05	21.78	7.06
10	กวาด บ้าน	**kwà:t bâ:n**	sweep floor	-12.035	0.549	13.73	21.92	7.20
11	ล้าง จาน	**lá:ŋ tɕa:n**	wash dishes	-4.659	0.212	5.30	21.98	7.26
12	ร้อง ไห้	**rɔ́:ŋ hâj**	cry	-6.090	0.277	6.93	21.99	7.27
13	รถ ไฟ	**rót faj**	train	-16.525	0.750	18.75	22.03	4.13
14	คน เก่ง	**kʰon kèŋ**	smart kid	-15.410	0.693	17.33	22.24	7.31
15	ยาง ลบ	**ja:ŋ lóp**	rubber	-6.705	0.297	7.43	22.58	7.52
16	นัก เรียน	**nák ri:an**	student	-12.480	0.543	13.58	22.98	7.86
17	ไข่ ไก่	**kʰàj kàj**	egg	-13.583	0.586	14.65	23.18	8.46
18	ถู พื้น	**tʰǔ: pʰúːn**	mop floor	-11.406	0.490	12.25	23.28	8.56
19	ห้อง นอน	**hɔ̂:ŋ nɔ:n**	bedroom	-10.848	0.465	11.63	23.33	8.61
20	ผูก เชือก	**pʰù:k tɕʰɯ̂:ak**	tie rope	-6.192	0.261	6.53	23.72	9.00
21	ซ้าย ขวา	**sá:j kʰwǎ:**	left right	-6.739	0.283	7.08	23.81	9.09
22	ตื่น เต้น	**tɯ̀:n tên**	excited	-11.022	0.457	11.43	24.12	9.40
23	หนัง สือ	**nǎŋ sɯ̌:**	book	-17.982	0.745	18.63	24.14	9.42
24	ใน หลวง	**naj lŭ:aŋ**	king	-11.385	0.468	11.70	24.33	9.61
25	ฝน ตก	**fŏn tòk**	rain	-11.143	0.452	11.30	24.65	9.93
		Mean		-9.628	0.430	10.76	22.23	7.51
		S.D.		3.59	0.15	3.72	1.56	1.56
		Min		-17.982	0.212	5.30	18.85	4.13
		Max		-4.659	0.750	18.75	24.65	9.93

[a]RI, regression intercept; [b]RS, regression slope; [c]Slope at 50%, Psychometric function slope (%/dB) at 50%; [d]Thres, Intensity required for 50% recognition; [e]ΔM dB, the difference between word threshold and mean PTA [of children] (14.72 dB HL)

a slope of 10.3%/dB for male speakers and 8.7%/dB for female speakers (20). In Thai, the mean psychometric function slope at 50% for recorded materials has been reported to be 9.0 %/dB for male speakers and 8.6 %/dB for female speakers (21). The mean psychometric function slope at 50% of selected Spanish materials for measurement of SRT in children has been reported to be 9.8%/dB for male speakers and of 8.3%/dB for female speakers (22).

As shown in the psychometric function graphs in Figure 3, the percentage of correct recognition increased from 0% to 100% within a small range of presentation intensity. From other similar studies of adults, the presentation level at 100% correctness was within 25 dB HL. However, the presentation level at 100% correct in this present study required an intensity higher than 25 dB HL, ranging from 28.16 dB HL to 43.65 dB HL with a mean of 34.13 dB HL (SD = 3.89) for all 25 spondee words. This is because the listeners were children rather than adults, i.e., they were much younger than participants in the other studies. For children, it may take a longer time and higher intensity than for adults to process and verbally respond to a word they have heard. Studies have shown that differences in the speed of processing between children and adults depends on their degree of brain development(23, 24). Furthermore, auditory discrimination was both lower and more inconsistent in children than in adults

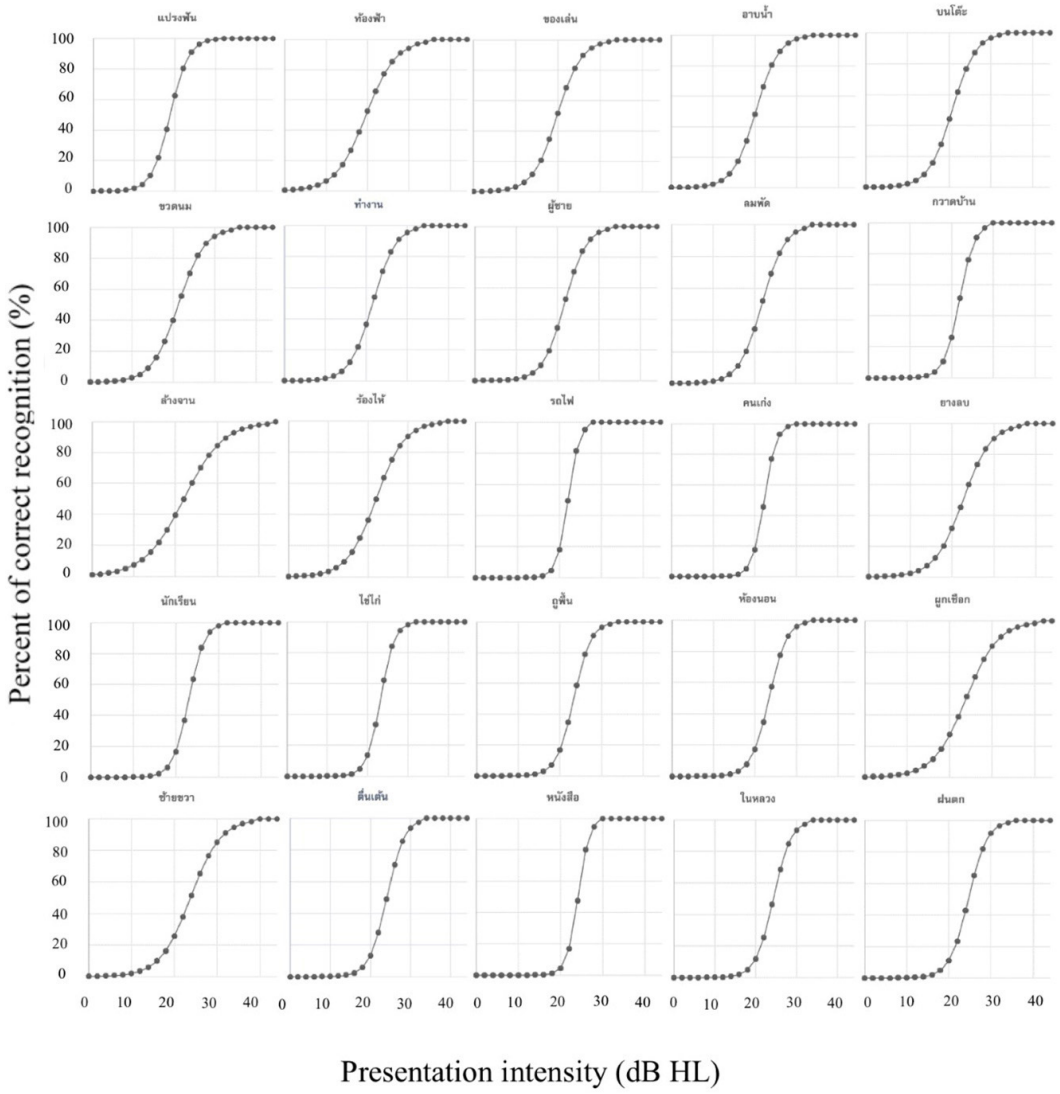

Figure 3. Psychometric function slopes for each of the 25 final spondee words and their data points

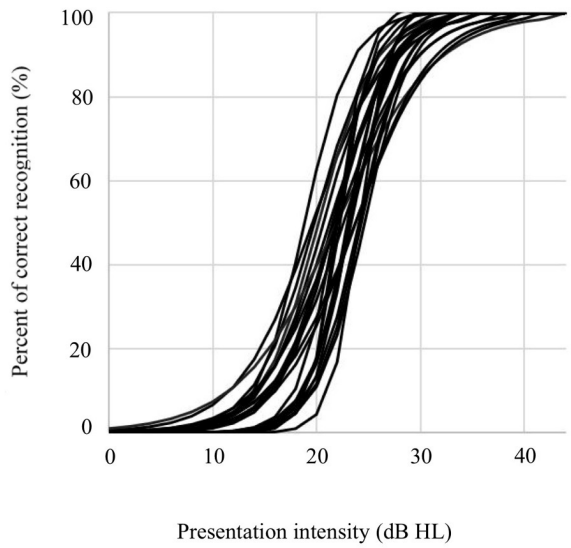

Figure 4. Psychometric function slopes for the final 25 spondee words

(25, 26). Nevertheless, the mean threshold of intelligibility of all 25 spondee words developed in this present study was 22.23 dB HL, which is within the 25 dB HL range.

This study was conducted in Bangkok which is located in the central region of Thailand. Although different dialects are spoken in each of the areas of Thailand, i.e., Central Thai, Northern Thai, Southern Thai, and Northeastern Thai, other studies indicate that dialect should not be a factor in SRT evaluation. A validation study of speech materials in Mainland Mandarin and Taiwanese Mandarin, mutually intelligible dialects, included SRT and WRS evaluation of single dialect speakers. That study showed a statistically significant difference in listener performance across material and

listener dialects, but clinical findings were statistically insignificant as differences were only minor (27). Additionally, a study of the effects of dialects on SRT measurements of children 6-7 years old reported that the differences in SRT results were non-significant between the dialects (28). Central Thai is the main dialect used by Thai people for oral communication, in public education as well as in most mass media in Thailand. For these reasons, the SRT materials developed in the present study are appropriate for use with children from all provinces of Thailand.

As a result of this present study, a new set of standardized speech recognition threshold materials (RAMA.SRT-3) for children was developed. This development was based on the following criteria: familiarity, phonetic dissimilarity, and homogeneity of audibility. This new set consists of 25 spondee words with an average threshold of intelligibility of about 22 dB HL having a 7 dB difference in PTA. Although these materials have not yet been tried in actual speech recognition threshold evaluations, this RAMA. SRT-3 list was developed according to speech material criteria. Thus, the RAMA. SRT-3 list can be used to determine the speech recognition threshold of Thai children. Further studies using other pediatric populations, a larger number of children, and including additional modern words should be conducted to further improve materials for measuring the SRT of children.

FUNDING

This study received no funding.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. American Speech-Language-Hearing Association. Determining threshold level for speech [homepage on the Internet]. ASHA; 1988 [cited 2018 Nov 18]. Available from: http://www.asha.org/policy.
2. Hudgins CV, Hawkins JE, Karlin JE, Stevens SS. The development of recorded auditory tests for measuring hearing loss for speech. Laryngoscope 1947;57:57-89.
3. Luksaneeyanawin S. Linguistics research and Thai speech technology. The 5th International conference on Thai studies; 1993 Jul 5-10; School of Oriental and African Studies. London: University of London; 1993.
4. Thathong U, Jitapunkul S, Ahkuputra V, Maneenoi E, Thampanitchawong B. Classification of Thai consonant naming using Thai tone. Proceeding of the 6th International Conference on Spoken Language Processing; 2000 Oct 16-20; Beijing: International Speech Communication Association; 2000.
5. Hirsh IJ, Davis H, Silverman SR, Reynolds EG, Eldert E, Benson RW. Development of materials for speech audiometry. J Speech Hear Disord. 1952;17: 321-37.
6. Amatyakul P. Audiology.Bangkok: Faculty of Medicine Ramathibodi Hospital, Mahidol University; 1973.
7. Kangsanarak B. Development of Thai spondee words for speech audiometry [Thesis]. Nakhon Pathom: Faculty of Graduate Studies, Mahidol University; 1980.
8. Northern JL, Downs MP. Hearing in children. 6th ed. San Diego: Plural; 2014.
9. Fior R. Physiological maturation of auditory function between 3 and 13 years of age. Audiology. 1972;11:317-21.
10. Graham JL. Psychometrically equivalent trisyllabic words for testing Spanish pediatric speech recognition thresholds [Thesis]. Utah: Brigham Young University; 2016.
11. Punch JL, Howard MT. Spondee recognition threshold as a function of set size. J Speech Hear Disord. 1985;50:120-5.
12. Meyer TA, Bilger RC. Effect of set size and method on speech reception thresholds in noise. Ear Hear. 1997;18:202-9.
13. Academic Department. Ministry of Education. Thai fundamental word list in teaching and learning Thai language for the first level (Primary 1-3). Bangkok: Ministry of Education; 1989.
14. Champaiboon T. Vocabulary in Thai textbooks: A corpus-based study. Nida Dev J. 2018; 58:23-51.
15. Ministry of Public Health. Developmental surveillance and promotion manual. Nonthaburi: Ministry of Public Health; 2014.
16. Ramkissoon I. Speech recognition thresholds for multilingual populations. Communication Disorders Quarterly. 2001;22:158-62.
17. Young Jr LL, Dudley B, Gunter MB. Thresholds and psychometric functions of the individual spondaic words. J Speech Lang Hear Res. 1982;25:586-93.
18. Wilson RH, Strouse A. Psychometrically equivalent spondaic words spoken by a female speaker. J Speech Lang Hear Res. 1999;42:1336-46.
19. Nissen SL, Harris RW, Slade KB. Development of speech reception threshold materials for speakers of Taiwan Mandarin. Int J Audiol. 2007;46:449-58.
20. Mangum TL. Performance intensity functions for digitally recorded Japanese speech audiometry

materials [Thesis]. Utah: Brigham Young University; 2005.
21. Hart A. Development of Thai speech audiometry materials for measuring speech recognition thresholds [Thesis]. Utah: Brigham Young University; 2008.
22. Graham JL. Psychometrically equivalent trisyllabic words for testing Spanish pediatric speech recognition thresholds [Thesis]. Utah: Brigham Young University; 2016.
23. Kail R. Developmental change in speed of processing during childhood and adolescence. Psychol Bull. 1991;109:490.
24. Kiselev S, Espy KA, Sheffield T. Age-related differences in reaction time task performance in young children. J Exp Child Psychol. 2009;102:150-66.
25. Nissen SL, Harris RW, Slade KB. Development of speech reception threshold materials for speakers of Taiwan Mandarin. Int J Audiol. 2007;46:449-58.
26. Buss E, III JWH, Grose JH. Psychometric functions for pure tone intensity discrimination: slope differences in school-aged children and adults. J Acoust Soc Am. 2009;125:1050-8.
27. Nissen SL, Harris RW, Channell RW, Richardson NE, Garlick JA, Eggett DL. The effect of dialect on speech audiometry testing. Am J Audiol. 2013;22:233-40.
28. Schneider BS. Effect of dialect on the determination of speech-reception thresholds in Spanish-speaking children. Lang Speech Hear Serv Sch. 1992;23:159-62.

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The Effect of Listening to Music on Stress Reduction among Twelfth-grade Students

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ABSTRACT

OBJECTIVE To examine the effects of listening to music on stress reduction among twelfth-grade students.

METHODS A quasi-experimental study was conducted with 116 twelfth-grade students recruited from a public school in Bangkok, Thailand, of whom 82 completed the study. During a 20-minute period, an intervention group (47 students) listened to music drawing upon nature sounds, while a control group (35 students) read about stress reduction techniques. Measurements were made of heart rates and stress levels using the Thai Stress Test (TST) and a 5-point Likert scale (stress 5-PL) at baseline and immediately after the activities. The t-test and chi-squared test for linear-by-linear association were used to compare changes in the stress parameters.

RESULTS Analysis of the baseline and post-intervention data revealed that music listening significantly reduced heart rates and scores for TST and stress 5-PL (p = < 0.001, 0.016, and < 0.001, respectively). However, reading about stress reduction produced no significant lowering of heart rates or scores for TST and stress 5-PL (p = 0.057, > 0.999, and 0.070, respectively). In a comparison between the groups, there were no significant differences in the reductions in heart rates or scores for TST and stress 5-PL (p = 0.490, 0.182, and 0.199, respectively).

CONCLUSIONS Listening to music for 20 minutes significantly decreased both physical and psychological stress, but the reduction did not differ from that achieved by reading about stress reduction.

KEYWORDS stress, music listening, students, adolescents, relax

INTRODUCTION

Stress is the body's reaction to changes that require physical and mental responses (1, 2). Appropriate stress levels allow individuals to be alert and prepared. On the other hand, excessive stress can lead to physical and mental illnesses (3).

Adolescence-the transitional stage of development between childhood and adulthood-is a critical period of change (4, 5). During that time, the brain, behavior, and hormonal systems undergo heightened remodeling (6). Additionally, the challenges of relationships, academic expectations, and the responsibilities to the family render adolescents vulnerable to stress (3).

A previous study of twelfth-grade students from a public school in Bangkok, Thailand, found that most students (66.2%) had an above-average level of stress. More specifically, slightly higher-than-average stress was experienced by 51.4% of the students, moderately higher-than-average stress by 12.6%, and much higher-than-average stress by 2.2% (7).

Another study in Thailand also reported a positive correlation between adolescents' stress levels and depressive symptoms (5). Stress in

adolescents has also been associated with suicide attempts (3, 8). Therefore, stress reduction intervention is important for Thai high-school students.

Music has been shown to beneficially affect stress-related physiological (9, 10), cognitive, (11) and emotional processes (12,13). Vibroacoustic therapy has also been used for the treatment of insomnia, anxiety disorders, self-injurious behavior, challenging behavior, autism, depression, and stress (14).

Several hypotheses about the mechanism of stress reduction by listening to music have been proposed. First, the music rhythm alters emotions as well as physiological functioning, e.g., heart rate, muscle tone, blood pressure, and respiration (15, 16). The sound is converted into electrical impulses which are sent by the reticular activating system (RAS) in the brain stem to the thalamus before being relayed to multiple areas of the cerebral cortex, cerebellum, corpus callosum, limbic system, and neuroendocrine systems (14, 17). Furthermore, the autonomic nervous system under the influence of music exhibits a relaxation response which can be seen in the alpha brain wave frequency observed on an electroencephalogram, and by a physiological manifestation: a state of muscular relaxation with regular, deep breathing and a lowered heart rate and blood pressure (18).

A meta-analysis study found that listening to either participants' own choice of music or relaxation music could reduce physiological stress (effect size = 0.285 and 0.393, respectively) and psychological stress (effect size = 0.521 and 0.609, respectively) (19). Characteristics of relaxing music include a constant rhythm with a 60–80 beats/min tempo, a frequency of 600-900 Hz, and little change in dynamics (14, 19). Twenty minutes is the minimum duration of music listening that has been associated with stress reduction (20).

Music listening is an interesting stress management method because of its simplicity, non-invasive approach, and cost-effectiveness. However, previous studies on the effect of music listening on adolescent stress in Thailand are limited. We therefore conducted this study to examine the effectiveness of listening to music in reducing the stress levels of twelfth-grade Thai students.

METHODS

Study design

This quasi-experimental study was registered in Thai Clinical Trials Research (TCTR 20210126001) and conducted in January 2020.

Participants and recruitment

The study took place at a public school (Chinorotwittayalai School) in Bangkok, Thailand. The researcher explained details of the investigation to students and faculty at the school. Twelfth-grade students who were able to read, write, and understand Thai were invited to participate, while students with a hearing impairment were excluded. Before commencement of the study, the formal assent of the participants was obtained in addition to parental consent.

A total of 184 students were initially enrolled (Figure 1). Of that number, 68 students did not meet the inclusion criteria, leaving 116 available for the study who were randomly assigned in equal numbers to an intervention and a control group (58 students each). Unfortunately, a number of students did not attend the study activity session so only 47 participants received the music intervention, while 37 participants were in the control group, a total of 82 students.

Interventions

Participants were asked to provide basic demographic data via a self-report questionnaire. Before the session activity commenced, their heart rates were measured with a handheld pulse oximeter (MD300M, ChoiceMMed, Beijing, China) to establish baseline values.

The members of the intervention group listened to relaxing piano pieces with nature sounds as a background composed by Chamras Saewataporn. The pieces were entitled "Rainbow", "Strolling in the Garden", "Butterflies and Flowers", "Fog", "Fly to Imagination", and "Forest Wind". All had a constant rhythm of 60-80 beats/min (14). Each participant could adjust the volume of the compositions via their smartphones to suit their individual preferences. The researcher provided participants with download link for the relaxing music to the intervention group. They were asked to rest, follow the flow of the relaxing music for 20 minutes, and not to sleep or do any other activity.

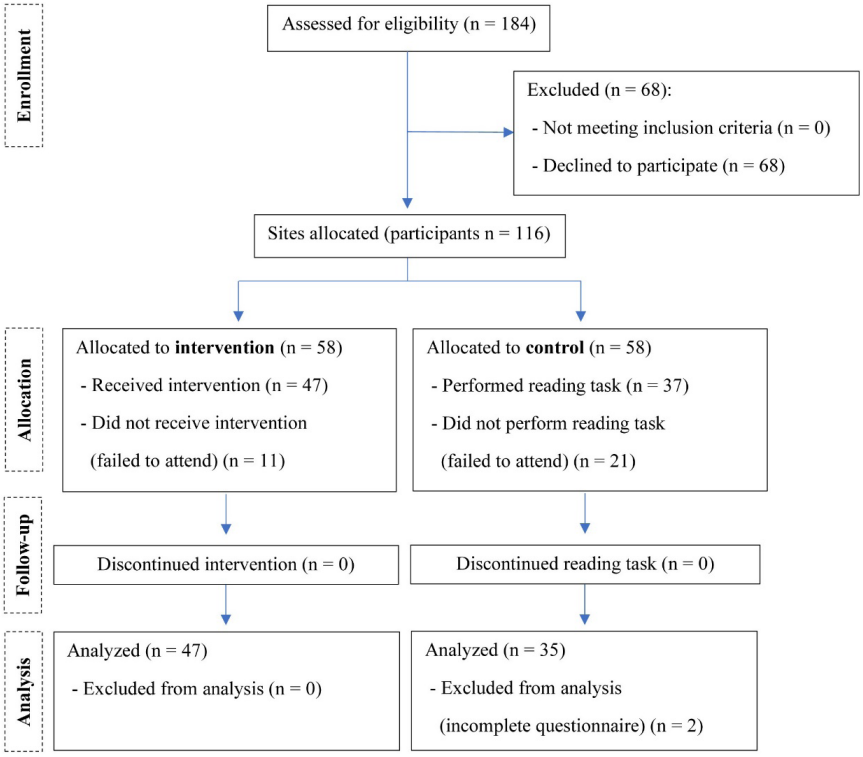

Figure 1. Study flowchart

Concurrently, the control group spent the 20 minutes reading about stress reduction methods provided by the research assistants. Participants in the intervention and control groups sat in separate meeting rooms which were quiet and calm.

Upon conclusion of the assigned activities, the heart rates of all participants were remeasured, and they were asked to again complete the questionnaires.

Outcome measurements

Primary outcome: stress reduction

The students' stress reduction was assessed by both physiological and psychological testing. Stress reduction was measured by change of heart rate, Thai Stress Test (TST) scores and a 5-point Likert scale (stress 5-PL) from baseline to post intervention.

A physiological response to stress, the heart rate was measured by a pulse oximeter at baseline and immediately after the completion of the session activity (16).

The TST and stress 5-PL were used to determine the level of psychological stress. The TST was developed by Phattharayuttawat et al. of the Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand (21) based on the results of a study of individuals ranging in age from 12 to 60 years. The 24 items of the TST have high construct validity and reliability. The alpha reliability coefficient of the total test is 0.84, and the subscale alpha values range between 0.85 and 0.91. The construct validity of the test consists of 2 factors: negative and positive scales. The values of the 2 scales range from 0.83 to 0.86. In addition, the split-half reliability coefficient of the total test is 0.88.

As to the stress 5-PL, the participants were asked to report their stress level at the time of the assessment by assigning a numerical score in response to the statement, "At this moment, I feel stressed". The score range was 0-4, with a higher score signifying a greater degree of stress (22, 23).

Secondary outcome: music genre

We asked the participants to indicate their favorite music genre by adding this open question to the questionnaire.

Sample size

A previous study of 770 Thai students revealed that two-thirds had higher-than-normal levels of stress (7). In the current investigation, it was estimated that, following the intervention,

the percentage of participants with a higher-than-normal stress level would be 33%, compared with 65% for the members of the control group. Using a 2-sided type I error of 0.05 and an 80% power, 38 samples per group were required. We therefore decided to recruit 42 samples for each group to compensate for the possibility of a 10% participant loss.

Allocation

Participants were allocated equally to the intervention and control groups by purposive sampling. The proportions of science- and art-program students were controlled so that they were the same in each group.

Statistical analysis

Demographic data and favorite music genre are presented using descriptive statistics. The pretest and posttest heart rates, TST scores, and stress-5-PL ratings were compared both within the same group and between the intervention and control groups. Pearson's chi-square test and Fisher's exact test were used to compare the categorical variables of the 2 groups, while the chi-squared test for linear-by-linear association was used for ordinal variables. A paired t-test and the Wilcoxon signed-rank test were used to test the differences between the pretest and posttest values for variables with and without normal distribution, respectively. In addition, an independent t-test was employed to test the differences between the intervention and control groups.

To account for the differences in the baseline data of the intervention and control groups, multiple linear regression was employed for the quantitative outcome, i.e., the heart-rate difference, whereas multiple logistic regression was utilized to analyze the binary outcomes, i.e., reductions in the stress-5-PL and TST values. The data analyses were performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, N.Y., USA). Two-tailed p-values of less than 0.05 were deemed statistically significant.

Ethical considerations

Prior to the implementation of the study, ethical approval was obtained from the Siriraj Institutional Review Board (COA: Si 843/2019). The students were provided with a full explanation of the study and were invited to participate. Confidentiality and anonymity were strictly observed. Informed consent to participate was obtained from all participants. Participants were advised that they had the right to withdraw at any time during the study, and that non-participation would not have any detrimental effect on their academic results or academic services received.

RESULTS

A total of 184 students were reviewed for eligibility (Figure 1). After exclusions and losses, 82 participants completed the study. The demographic characteristics of the 2 groups are detailed in (Table 1). Most participants were 18-year-old women with a grade point average (GPA) of more than 2.5. Their main sources of stress were study and their upcoming university (college) entrance examinations. The students in the 2 groups demonstrated no statistically significant differences in age or in their most stressful issues; however, there were statistically significant differences in the sex and GPAs of the intervention and control groups. However, sex and GPA level were not significantly associated with stress level changes in a multiple linear regression analysis of heart rate differences (Table 2) and a multiple logistic regression analysis of the value differences for TST (Table 3) and stress 5-PL (Table 4). A baseline comparison of the stress parameters of the intervention and control groups found they were not statistically different (Table 1).

The pretest-posttest score comparison of the intervention group indicated that there was a significant reduction in heart rate and in the scores for TST and stress 5-PL (p = < 0.001, 0.016, and < 0.001, respectively). In contrast, the pretest-posttest score comparison for the control group found no significant differences in the heart rates and the TST and stress-5-PL scores (p = 0.057, > 0.999, and 0.070, respectively). There were also no significant differences in the mean heart rates, TST scores, and stress-5-PL ratings of the 2 groups (p = 0.490, 0.182, and 0.199, respectively) (Tables 5, 6 and 7).

The favorite music genres of the intervention group were popular music (31.7%), rhythm and blues (17.1%), rap (7.3%), rock (4.9%), hip

Table 1. Demographic and clinical characteristics of intervention and control groups (n=82)

Demographics	Group			*p*-value
	Total (n=82)	Music (n=47)	Control (n=35)	
Sex, n (%)				
Male	30 (36.6)	22 (46.8)	8 (22.9)	0.026[χ]
Female	52 (63.4)	25 (53.2)	27 (77.1)	
Age (years), n (%)				
17	5 (6.1)	5 (10.6)	0	0.099[γ]
18	73 (89.0)	39 (83.0)	34 (97.1)	
19	4 (4.9)	3 (6.4)	1 (2.9)	
Grade point average, n (%)				
≤ 2.50	4 (4.9)	1 (2.1)	3 (8.6)	0.019[γ]
2.51–3.00	25 (30.5)	10 (21.3)	15 (42.9)	
3.01–3.50	29 (35.4)	17 (36.2)	12 (34.3)	
3.51–4.00	24 (29.3)	19 (40.4)	5 (14.3)	
Most stressful issue in the past month, n (%)				
Studying	17 (21.3)	7 (14.9)	10 (30.3)	0.222[γ]
Entrance examination	40 (50.0)	27 (57.4)	13 (39.4)	
Peer relationships	2 (2.5)	1 (2.1)	1 (3.0)	
Family relationships	4 (5.0)	2 (4.3)	2 (6.1)	
Love	2 (2.5)	2 (4.3)	0	
Finances	9 (11.3)	3 (6.4)	6 (18.2)	
Health	2 (2.5)	2 (4.3)	0	
Other	4 (5.0)	3 (6.4)	1 (3.0)	
Baseline heart rate				
Mean (SD)	81.4 (9.9)	80.5 (9.5)	82.6 (10.4)	0.345[δ]
Baseline TST, n (%)				
Excellent mental health	1 (1.2)	1 (2.1)	0	> 0.999[γ]
Normal mental health	31 (37.8)	18 (38.3)	13 (37.1)	
Mild stress	47 (57.3)	26 (55.3)	21 (60.0)	
Stressed	3 (3.7)	2 (4.3)	1 (2.9)	
Baseline Stress (5-PL), n (%)				
0	10 (12.2)	9 (19.1)	1 (2.8)	0.153[γ]
1	17 (20.7)	7 (14.9)	10 (28.6)	
2	31 (37.8)	17 (36.2)	14 (40.0)	
3	20 (24.4)	12 (25.5)	8 (22.9)	
4	4 (4.9)	2 (4.3)	2 (5.7)	

[χ], Pearson's chi-squared test; [γ], Fisher's exact test; [δ] Independent t-test;
SD, standard deviation; TST, Thai Stress Test; stress (5-PL), 5-point Likert scale; *p*-value < 0.05

Table 2. Results of multiple linear regression of heart-rate differences (post-pre)

	b*	SE(b)	*p*-value
Group			
Control	-	-	-
Music	-2.841	1.875	0.134
Sex			
Female	-	-	-
Male	1.139	1.831	0.536
GPA			
≤ 3.00	-	-	-
3.01-3.5	0.15	2.022	0.762
3.51-4.00	0.901	2.298	0.696

b*, linear regression coefficient; GPA, grade point average; SE, standard error; *p*-value < 0.05

hop (4.9%), jazz (2.4%) and other (31.7%). The favorite music genres of the control group were popular music (35.4%), rhythm and blues (9.7%), rock (9.7%), indie (8.1%), rap (6.5%), classical (3.2%), and other (27.4%).

DISCUSSION

This study was conducted to examine the effects of listening to music on the stress response of twelfth-grade students. It was hypothesized that participants in the intervention group would show a greater stress reduction than those in the control group. The results found that the participants who listened to music had a greater decrease in heart rate and

Table 3. Multiple logistic regression analysis of reduction in Thai Stress Test scores

	Change in stress		Univariable analysis		Multivariable analysis	
	No decrease*	Decrease	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Group, n (%)						
Control	31 (88.6)	4 (11.4)	1		1	
Music	40 (85.1)	7 (14.9)	1.36 (0.36-5.05)	0.65	1.03 (0.22-4.80)	0.966
Sex, n (%)						
Female	48 (92.3)	4 (7.7)	1		1	
Male	23 (76.7)	7 (23.3)	3.65 (0.97-13.74)	0.055	3.35 (0.75-14.98)	0.113
GPA, n (%)						
≤ 3.00	25 (86.2)	4 (13.8)	1		1	
3.01-3.50	23 (79.3)	6 (20.7)	1.63 (0.41-6.52)	0.489	1.81 (0.41-7.98)	0.430
3.51-4.00	23 (95.8)	1 (4.2)	0.27 (0.03-2.61)	0.259	0.34 (0.03-3.58)	0.368

No decrease*, either no change or increase in stress levels; GPA, grade point average; *p*-value < 0.05

Table 4. Multiple logistic regression of reduction in stress scores for 5-point Likert scale (5-PL)

	Change in stress		Univariable analysis		Multivariable analysis	
	No decrease*	Decrease	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Group, n (%)						
Control	28 (80.0)	7 (20.0)	1		1	
Music	35 (74.5)	12 (25.5)	1.38 (0.48–3.94)	0.558	1.45 (0.42–4.98)	0.553
Sex, n (%)						
Female	41 (78.8)	11 (21.2)	1		1	
Male	22 (73.3)	8 (26.7)	1.36 (0.48–3.86)	0.569	1.13 (0.34–3.76)	0.840
GPA, n (%)						
≤ 3.00	24 (82.8)	5 (17.2)	1		1	
3.01-3.50	18 (62.1)	11 (37.9)	2.93 (0.87–9.95)	0.084	2.76 (0.79–9.71)	0.113
3.51-4.00	21 (87.5)	3 (12.5)	0.69 (0.15–3.22)	0.633	0.61 (0.11–3.25)	0.559

No decrease*, no change or increase in stress levels; GPA, grade point average; *p*-value < 0.05

Table 5. Heart rates of intervention and control groups

Heart rate	Mean (SD)		*p*-value
	Music (n=47)	Control (n=35)	
Pre	80.5 (9.5)	82.6 (10.4)	-
Post	75.5 (9.7)	79.9 (10.9)	-
Post-Pre	-4.9 (6.8)	-2.6 (7.9)	0.160[δ]
p-value	< 0.001[t]	0.057[t]	-

[δ], Independent t-test; [t], Paired t-test; SD, standard deviation; *p*-value < 0.05

TST and stress 5-PL scores than those in the control group, but the differences were not statistically significant. Despite the differences in the sex and GPA profiles of the participants in the 2 groups, multiple linear regression (Table 2) and a multiple logistic regression (Table 3 and 4) determined that those factors did not influence the changes in stress levels.

Comparison with other studies

Previous studies have reported that listening to music significantly reduces stress, both physically and psychologically (15, 24-26). The contradiction of the results between the previous studies and the current investigation can be explained in several ways.

First, the populations of previous studies were adults and included unhealthy individuals (24, 26), whereas the participants in our study were all healthy adolescents.

In addition, the duration of the intervention in Han's study (26) was 30 minutes, while in our study it was 20 minutes. Nevertheless, research has found that 20 minutes of listening to music is sufficient to achieve a significant decrease in stress levels (20).

Moreover, the participants in the control group in Han's study (26) were asked to rest,

Table 6. Thai Stress Test of intervention and control groups (n=82)
(a) Comparison of pre- and post-intervention stress levels of each group

Thai stress test (TST), n	Music			Control		
	Pretest (n=47)	Posttest (n=47)	*p*-value	Pretest (n=35)	Posttest (n=35)	*p*-value
Excellent mental health	1	5	< 0.016[φ]	0	1	> 0.999[φ]
Normal mental health	18	17		13	12	
Mild stress	26	23		21	21	
Stressed	2	2		1	1	

(b) Comparison between the changes in the stress levels of the 2 groups

TST difference (pre-post), n (%)	Music (n=47)	Control (n=35)	*p*-value
-1 (stress elevation)	0 (0)	3 (8.6)	0.182[c]
0 (no change)	40 (85.1)	28 (80)	
1 (stress reduction)	7 (14.9)	4 (11.4)	

[φ], Wilcoxon signed-rank test; [c], chi-squared test for linear-by-linear association; *p*-value < 0.05

Table 7. Stress (5-point Likert scale) of the intervention and control groups (n=82)
(a) Comparison of the pre- and post-intervention stress levels of each group

Stress test (5-PL), n	Music			Control		
	Pretest (n=47)	Posttest (n=47)	*p*-value	Pretest (n=35)	Posttest (n=35)	*p*-value
0 (no stress)	9	11	< 0.001[φ]	1	2	0.070[φ]
1	7	12		10	11	
2	17	16		14	14	
3	12	7		8	7	
4 (most stress)	2	1		2	1	

(b) Comparison of changes in stress levels between the 2 groups

Difference in stress (5-PL) (pre-post), n (%)	Music (n=47)	Control (n=35)	*p*-value
-1 (stress elevation)	0 (0)	1 (2.9)	0.199[c]
0 (no change)	35 (74.5)	27 (77.1)	
1 (mild stress reduction)	9 (19.1)	7 (20)	
2 (moderate stress reduction)	2 (4.3)	0 (0)	
3 (high stress reduction)	1 (2.1)	0 (0)	

[φ], Wilcoxon signed-rank test; [c], chi-squared test for linear-by-linear association; Stress (5-PL), 5-point Likert scale; *p*-value < 0.05

while the control group members in the present work were asked to read information about stress reduction. By assigning the reading task, we aimed to reduce the likelihood that our control group members would become distracted by some other activity, such as a physical activity. On the other hand, resting without doing any activity (such as reading) might inadvertently increase stress levels by making individuals feel like they are being imprisoned or confined. A meta-analytic review found that psychoeducation had a positive effect on stress reduction with a small effect size (standardized mean difference = 0.27) (27). The intervention in one of the studies examined in that meta-analysis, namely, by Cousineau, involved providing educational material only once and for a short period, which is similar to the intervention in the present article. The research by Cousineau found no significant effects of psychoeducation on stress reduction.

Finally, as the baseline stress levels of the participants in the current study were mild, the pretest-posttest score changes might not have reached statistical significance.

Clinical implications

Listening to music that incorporates nature sounds might help to reduce mild stress, e.g., stress before an examination or a class presentation.

Strengths and limitations

The current work was conducted with adolescents. To date, there have been few studies of the effects of listening to music on stress reduction in adolescents. Moreover, the assessment measures used included both objective (heart rate) and subjective (self-rating questionnaire) elements.

On the other hand, the small sample size of the control group in the study may have lacked the statistical power needed to determine the effectiveness of the intervention. Having a larger sample size is recommended for further studies. Moreover, there was no statistically significant difference in the stress reduction scores of the groups. As the TST scores showed that 40% of participants had a normal stress level at baseline, there may have been a ceiling effect for the stress reduction resulting from the intervention. The differences in the favorite music genres of the 2 groups and the percentage of participants favored popular music in the intervention group may have also affected the results. Additionally, the reading of the stress reduction material by the members of the control group might in itself have had a stress-lowering effect, even though that influence was not statistically significant. Rather than reading stress-reduction literature, using a control condition which does not impact on stress levels is advised for future studies. Doing so may provide an increased opportunity to identify statistically significant differences in stress reduction scores of the groups and thus reveal the true effects of listening to music. In addition, this study used per-protocol analysis to analyze the results. We did not use intention-to-treat analysis because 32 participants (27.6%) from both groups did not come to school and failed to participate in the music listening or stress management reading activities. They also did not complete any of the questionnaires. The amount of missing data might have affected the reliability of the results interpretation using intention-to-treat analysis. The results of our study could represent only the efficacy of the intervention. Further study of the effectiveness is required.

CONCLUSIONS

Listening to music for 20 minutes can significantly reduce both physical and psychological stress. However, the reduction in stress from listening to music for 20 minutes does not differ from that achieved by reading about stress reduction methods for the same period.

FINANCIAL DISCLOSURE

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DECLARATION OF COMPETING INTERESTS

None

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REFERENCES

1. Miryala RK. Trends, challenges & innovations in management - volume III. Telangana: Zenon Academic Publishing; 2015.
2. Ojha U. managing teen stress. Psychosocial aspect of health and illness. Delhi: Global Vision Publishing House; 2015.
3. Chandra A, Batada A. Exploring stress and coping among urban African American adolescents: the shifting the lens study. Prev Chronic Dis. 2006;3: A40.
4. Jayanthi P, Thirunavukarasu M, Rajkumar R. Academic stress and depression among adolescents: a cross-sectional study. Indian Pediatr. 2015;52: 217-9.

5. Maritta V, Ruthaychonnee S, Minna A. Survey of adolescents' stress in school life in Thailand: implications for school health. J Child Health Care. 2017;21:222-30.
6. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000;24:417-63.
7. Dechkum K. A study of stress of Mathayom Suksa six students during the economic crisis. Bangkok: Chulalongkorn University; 1998.
8. Vo D, Park MJ. Stress and Stress Management Among Youth and Young Men. Am J Mens Health. 2009;2:353-66.
9. Khalfa S, Bella SD, Roy M, Peretz I, Lupien SJ. Effects of relaxing music on salivary cortisol level after psychological stress. Ann N Y Acad Sci. 2003; 999:374-6.
10. Nater UM, Abbruzzese E, Krebs M, Ehlert U. Sex differences in emotional and psychophysiological responses to musical stimuli. Int J Psychophysiol. 2006;62:300-8.
11. Burns J, Labbé E, Williams K, McCall J. Perceived and physiological indicators of relaxation: as different as Mozart and Alice in chains. Appl Psychophysiol Biofeedback. 1999;24:197-202.
12. Juslin P, Sloboda J. Handbook of music and emotion: theory, research, applications. Oxford: Oxford University Press; 2010.
13. Jacobsen SL, Pedersen IN, Bonde LO, Odell-Miller H. A comprehensive guide to music therapy, 2nd Edition: theory, clinical practice, research and training. London: Jessica Kingsley Publishers; 2019.
14. Bonde LO, Wigram T. A comprehensive guide to music therapy: theory, clinical practice, research and training. London: Jessica Kingsley Publishers; 2002.
15. Chlan L. Music therapy as a nursing intervention for patients supported by mechanical ventilation. AACN Clinical Issues. 2000;11:128-38.
16. Solanki MS, Zafar M, Rastogi R. Music as a therapy: role in psychiatry. Asian J Psychiatr. 2013;6:193-9.
17. Watkins G. Music therapy: proposed physiological mechanisms and clinical implications. Clin Nurse Spec. 1997;11:43-50.
18. Lee O, Chung Y, Chan M, Chan W. Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study. J Clin Nurs. 2005;14:609-20.
19. de Witte M, Spruit A, van Hooren S, Moonen X, Stams G-J. Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. Health Psychol Rev. 2020;14: 294-324.
20. Linnemann A, Wenzel M, Grammes J, Kubiak T, Nater U. Music listening and stress in daily life-a matter of timing. Int J Behav Med. 2017;25: 223-30.
21. Phattharayuttawat S, Ngamthipwathana T, Sukhatungkha K. The development of the Thai Stress Test. 2000;45:237-50.
22. Elo A-L, Leppänen A, Jahkola A. Validity of a single-item measure of stress symptoms. Scand J Work Environ Health. 2004;29:444-51.
23. Linnemann A, Ditzen B, Strahler J, Doerr J, Nater U. Music listening as a means of stress reduction in daily life. Psychoneuroendocrinology. 2015;60: 82-90
24. Allen K, Golden LH, Izzo JL, Jr., Ching MI, Forrest A, Niles CR, et al. Normalization of hypertensive responses during ambulatory surgical stress by perioperative music. Psychosom Med. 2001;63:487-92.
25. Thoma M, Marca R, Brönnimann R, Finkel L, Ehlert U, Nater U. The effect of music on the human stress response. Plos One. 2013;8:e70156.
26. Han L, Li JP, Sit JW, Chung L, Jiao ZY, Ma WG. Effects of music intervention on physiological stress response and anxiety level of mechanically ventilated patients in China: a randomised controlled trial. J Clin Nurs. 2010;19:978-87.
27. Van Daele T, Hermans D, Audenhove C, Van den Bergh O. Stress reduction through psychoeducation a meta-analytic review. Health Educ Behav. 2012;39:474-85.

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Impact of Intraoperative Ultrafiltration on the Development of Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Cardiac Surgery

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ABSTRACT

OBJECTIVE To evaluate the incidence and effectiveness of using ultrafiltration in chronic kidney disease (CKD) patients during cardiac surgery.

METHODS A retrospective record review of all chronic kidney disease patients who underwent cardiac surgery at a university hospital medical center in Thailand from January 2013 to December 2018.

RESULTS Data from 306 eligible CKD patients were analyzed. The average age of patients was 63.89 ± 10.05 years. Two-hundred and twenty-two patients were male (72.2%). More than half of the patients (162/306 or 52.9%) underwent ultrafiltration (UF) during cardiopulmonary bypass (CPB). During the postoperative period, CKD patients who had received the UF were more likely to have higher postoperative serum creatinine after surgery and on postoperation day 1 ($p < 0.01$). However, there was no statistically significant difference in the occurrence of acute kidney injury (AKI) among CKD patients who received ultrafiltration and those who did not.

CONCLUSIONS In this study, the ultrafiltration intervention did not reduce the incidence of AKI among patients with CKD who underwent cardiac surgery during CPB. However, further prospective investigation is needed to fully evaluate the contribution of ultrafiltration in reducing the risk of developing postoperative AKI among patients with preexisting renal failure.

KEYWORDS ultrafiltration, chronic kidney disease, acute kidney injury, cardiac surgery

INTRODUCTION

Individuals with chronic kidney disease (CKD) undergoing cardiac surgery are placed in the high-risk category for acute kidney injury (AKI) (1). AKI is a renal function deterioration complication which can develop within 48 hours after cardiac surgery and can significantly increase the risk of postoperative morbidity and mortality. AKI can also increase the length of hospital stays and the cost of medical care. The incidence of cardiac surgery-associated AKI varies from 5 to 45% depending on the patient's preoperative diagnostic AKI criteria and the type of cardiac surgery (2). According to the previous studies, the occurrence of AKI has a complex pathophysiology with many risk factors such as perioperative hemodynamic alterations, comorbid condition, predisposing renal injury, reperfusion injury, hemolysis, inflammation, and pharmacological toxicity associated with cardiac surgery (3, 4).

Early recognition of patients at high-risk of developing postoperative AKI is essential to provide appropriate support and care. Creatinine clearance has been viewed as an important preoperative predictor of cardiac surgery outcome. Since the level of serum creatinine is dependent on body size and the state of dehy-

dration, it can indicate possible renal impartment in CKD patients (5, 6). Moreover, CKD patients of advanced age and those who have other comorbid conditions such as diabetes mellitus, hypertension, dyslipidemia, and chronic obstructive pulmonary disease are at a high risk of developing AKI (7, 8).

Cardiac surgery is commonly accompanied by a cardiopulmonary bypass (CPB) to temporarily support the heart and respiratory functions necessary to maintain the patient's blood circulation and oxygenation (9, 10). Inflammatory mediators are secreted into the CPB circulation due to the contact of blood with a non-epithelial foreign surface (11). These mediators may increase the total amount of fluid from the intravascular area passing through tissue, preventing organs and tissues from functioning normally (8). Excess fluid load during cardiac surgery is a leading cause of the higher incidence of death in CKD patients compare to patients without excessive fluid. AKI complication following cardiac surgery can be reduced by the application of preventive intervention by healthcare professionals during perioperative and intraoperative stages.

Ultrafiltration is the most practical technique for reducing hemodilution and preventing major organ dysfunction associated with CPB as it eliminates excessive prime volume, reduces fluid accumulation and systemic inflammatory response syndrome (12-15). Using this method, inflammatory cytokines and plasma-free water are eliminated by passing blood through a hemofilter containing a semipermeable membrane during ultrafiltration. Currently, conventional ultrafiltration (CUF) and modified ultrafiltration (MUF) are the two main techniques used in cardiac surgery. CUF can be performed during CPB to avoid hemodilution by removing volume of filtrate through a venous reservoir (16),while MUF is usually performed after separation from CPB and before decannulation (17). The MUF technique has been established as standard-of-care in the pediatric population (17). However, the benefit and risk of using ultrafiltration (either CUF or MUF) in adult cardiac surgical populations remains controversial.

According to the American Society of Extracorporeal Technology and the Society of Cardiovascular Anesthesiologists, fluid management and mechanical circulatory support using ultrafiltration should be monitored continually during CPB (18, 19). Recently, ultrafiltration has been implemented in a cardiovascular surgery center in Thailand. However, few studies have reported on the benefit of using ultrafiltration in CKD patients undergoing cardiac surgery. This retrospective study aimed to contribute to the ongoing research on kidney disease prevention among patients undergoing cardiac surgery.

OBJECTIVES

The objectives of this retrospective study were to evaluate the frequency of AKI and the effectiveness of ultrafiltration in reducing the incidence of AKI in CKD patients following cardiac surgery.

MATERIALS AND METHODS

Study design and patient selection

This retrospective study was conducted in accordance with the guidelines of the Helsinki Declaration after obtaining approval from the Chiang Mai University Faculty of Medicine Research Ethics Committee. The study utilized data from 306 CKD patients (stage 3-5) who had undergone cardiac surgery between January 2013 and December 2018.

Patient demographic data, co-morbidities, CPB, operation times, laboratory values, cross-clamp times, hospital stay duration, and complications were investigated retrospectively using patient medical records. In the perioperative period, the following parameters were examined: serum creatinine (Cr) (at admission then every 24 hours for a minimum of 48 hours), duration of CPB and cross-clamping, as well as the need for the renal replacement therapy (RRT) during the intensive care unit (ICU) stay, and AKI staging (see Table 1). In this study, AKI staging was classified according to Acute Kidney Injury Network (AKIN) criteria using changes in serum Cr alone (20).

Inclusion criteria

CKD patient inclusion criteria were:

1. Aged 18 years or older;
2. CKD at stage 3 or greater who underwent elective cardiac surgery;
3. Serum Cr levels > 1.5 mg/dL; and

Table 1. AKI staging by AKIN criteria

Stage	Serum creatinine (Cr) criteria	Urine output criteria
1	Increase in serum Cr of > 0.3 mg/dL or an increase to > 150 to 200% (1.5 to 2 fold) from baseline	< 0.5 mL/kg/hr > 6 hrs
2	Increase in serum Cr of > 200 to 300% (> 2 fold to 3 fold) from baseline	< 0.5 mL/kg/hr > 12 hrs
3	Increase in serum Cr of > 300% (> 3 fold) from baseline or serum Cr > 4 mg/dL with an acute increase of at least 0.5 mg/dL	< 0.3 mL/kg/hr for 24 hrs and least 0.5 mg/dL auria for 12 hrs

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; Cr, creatinine

4. Glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2

Exclusion criteria

CKD patients who met any of the following criteria were excluded from the study:

1. Under 18 years of age;
2. CKD patients at stage 1 and 2; or
3. Undergoing emergency surgery

Statistical analysis

Statistical analysis was performed using the SPSS for Windows, version 16.0 (Statistic Inc. version Chicago, IL, U.S.A.). Descriptive statistics are shown as mean ± standard deviation (SD) for continuous variables, and number plus percent for nominal variables. Chi-square test, Fisher's exact test, and ANOVA were used for comparing preoperative, intraoperative, and post-operative patient characteristics between patients who received ultrafiltration and those who did not. The results were considered statistically significant when $p < 0.05$, a 95% confidence interval.

RESULTS

The demographic data and preoperative features of the patients are summarized in Table 2. This retrospective study included 306 patients with CKD stage 3-5 who had undergone cardiac surgery. More than half of the patients (162/306 or 52.9%) also underwent ultrafiltration during CPB. The average age of the patient was 63.89 ± 10.05 years. Two-hundred and twenty-two patients were male (72.2%). Younger male patients with a history of CKD stage 3-5 were more likely to have received ultrafiltration during cardiac surgery than older patients and females ($p < 0.05$).

The incidence of AKI among CKD patients (stage 3-5) who underwent cardiac surgery is shown in Table 3. The number of patients with AKI associated cardiac surgery was 67 (20.9%). However, there was no statistically significant difference in the incidence of AKI between CKD patients who received ultrafiltration and those who did not (19.1%; 95% CI: 0.89–1.57 vs. 25.0%, 95% CI: 0.65–1.09, respectively; $p = 0.22$).

During the postoperative period (Table 4), CKD patients who received ultrafiltration were more likely to have higher postoperative serum Cr after surgery, post-operation day 1 and day 2 ($p < 0.01$). The average length of hospital stays among CKD patients who received ultrafiltration during cardiac surgery was 23.52 ± 24.42 days vs. 16.35 ± 12.87 days for those who did not receive ultrafiltration.

DISCUSSION

The ultrafiltration technique is one strategy for preventing major organ dysfunction associated with CPB by minimizing hemodilution effects, reducing fluid accumulation and reducing mediators that can initiate a systemic inflammatory response syndrome (15, 18).

This study found no statistically significant difference in the prevalence of AKI among CKD patients who received ultrafiltration and those who did not. This result is similar to a study by Boodhwani et al. (21) which similarly reported no significant benefit of the CUF technique after CPB. Additionally, Paugh et al. (18) reported that there was an increased risk of developing AKI after CPB among adult patients with baseline CKD. The present study found no difference in patient preoperative risk profiles between the two groups. As our study samples were cardiac patients with CKD stage 3 and 4, there was obvious selection bias because the average serum Cr level and CKD stage in the ultrafiltration group were higher than the

Table 2. Preoperative and intraoperative demographic characteristics among CKD patients

Variables	Ultrafiltration		*p*-value
	No	Yes	
Number of procedures	144 (47.1%)	162 (52.9%)	
Perioperative			
Age	65.26±9.63	62.66±10.28	0.02
Sex			
Male	105 (72.9%)	116 (71.6%)	0.79
Female	39 (27.1%)	46 (28.4%)	
BSA	1.60±0.18	1.59±0.17	0.66
Serum Cr level	1.80±0.28	3.91±2.82	< 0.001
Comorbid condition			
Diabetes Mellitus	50	71	0.10
Hypertension	92	108	0.61
Dyslipidemia	59	67	0.94
COPD	4	4	0.87
Pre-hemodialysis			
Yes	0 (0%)	32 (19.8%)	< 0.001
No	144 (100.0%)	130 (80.2%)	
CKD staging			
Stage 3 (n=169)	119 (82.6%)	50 (30.9%)	< 0.001
Stage 4 (n=74)	25 (17.4%)	49 (30.2%)	
Stage 5 (n=63)	0 (0%)	63 (38.9%)	
Intraoperative			
CPB time (min)	129.90±56.84	130.81±62.90	0.89
Cross-clamp time (min)	86.80±55.40	77.61±59.89	0.17

CKD, chronic kidney disease; BSA, body surface area; Cr, creatinine; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass

Table 3. Incidences of AKI among CKD patients after cardiac surgery

	No. of AKI cases	AKI incidences (%)	95% CI		*p*-value
			Upper	Lower	
Ultrafiltration	31	19.1	0.89	1.57	0.22
No-ultrafiltration	36	25.0	0.65	1.09	

AKI, acute kidney injury; CKD, chronic kidney disease

Table 4. Postoperative data for CKD patients

Variables	Ultrafiltration		*p*-value
	No (n=144)	Yes (n=162)	
RRT at ICU			
Yes	3 (2.1%)	11 (6.8%)	0.05
No	141 (97.9%)	151 (93.2%)	
Creatinine level			
Post-op day 0	1.64±0.43	2.99±1.95	< 0.001
Post-op day 1	2.03±0.52	3.76±2.29	< 0.001
Post-op day 2	2.27±0.77	3.98±2.17	< 0.001
Hospital stay (days)	16.35±12.87	23.52±24.42	< 0.01

CKD, chronic kidney disease; RRT, renal replacement therapy; ICU, Intensive Care Unit

non-ultrafiltration group. Fluid overload from CPB and excessive fluid removal during ultrafiltration intervention can negatively impact renal function. Using ultrafiltration in patients with CKD might increase the risk of developing AKI due to the greater infiltration volume as

well as to other baseline conditions of this group (22). The ultrafiltration group also have had acute kidney injury due to their cardiac condition which could have resulted in serum Cr and postoperative serum Cr being higher at every point in time. Changes in serum Cr show that the non-ultrafiltration group had elevated serum Cr until postoperative day 2, while serum Cr in the ultrafiltration group remained at baseline without elevation. The intermediate interoperative serum Cr level in the ultrafiltration group was lower than baseline but rose in postoperative day 2. The incidence of postoperative RRT in the ultrafiltration group was only 6.8% even though they had RRT preoperatively, while in non-ultrafiltration group there was no postoperative RRT despite no preoperative RRT. This might indicate that ultrafiltration can lessen or delay the impact of CPB which can contribute to renal dysfunction after cardiac surgery.

Ultrafiltration, however, might not have affected the overall clinical cost because the patients in ultrafiltration group on average had a longer hospital stay. Duration of surgery in our study could be a limitation because the mean CPB times of the non-ultrafiltration group and ultrafiltration group were 129.90 ± 56.84 min and 130.81 ± 62.90 min, respectively. The mean cross-clamp time of the non-ultrafiltration group and the ultrafiltration group were 86.80 ± 55.40 min and 77.61 ± 59.89 min, respectively. According to empirical studies, longer CPB time or cross-clamp time might impact the effectiveness of ultrafiltration. Previous studies have suggested that the risk of AKI can increase from 10-to 15-fold after 60 min of CPB (23, 24). Prolonged cross clamp time might increase the risk of low cardiac output, unfortunately, the definitive safe period of time for clamping remains undefined (25).

LIMITATIONS

First, it is acknowledged that this study was limited, as any retrospective study is, by the low number of patients and thus also less data on urine output and mortality rate as well. Nevertheless, there are some questions that cannot be answered based on the available data: are there risk factors associated with postoperative AKI such as nadir oxygen delivery, hematocrit level during and after operation, and the amount of transfusion during ultrafiltration. These and other associated potential risk factors should be a focus of future study. Secondly, the majority of CKD patients were males and living in Northern Thailand, which limits generalization of finding to CKD patients to females and to individuals living in other areas of Thailand and in other countries. Lastly, this study presents the unique experience in one cardiovascular center, further large, multicenter observational study are needed.

CONCLUSIONS

Ultrafiltration intervention does not reduce the risk of AKI among patients with CKD who undergo cardiac surgery during CPB. Further prospective investigation is needed to more fully evaluate the contribution of ultrafiltration to reducing the risk of postoperative AKI among patients with preexisting renal failure. Prospective studies in adult cohorts with higher disease severities are needed to determine the relationship between the ultrafiltration technique and other potential risk factors for developing AKI following cardiac surgery.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to disclose.

REFERENCES

1. Vellinga S, Verbrugghe W, De Paep R, Verpooten GA, Janssen van Doorn K. Identification of modifiable risk factors for acute kidney injury after cardiac surgery. Neth J Med. 2012;70:450-4.
2. Skarupskienė I, Adukauskienė D, Kuzminskienė J, Rimkutė L, Balčiuvienė V, Žiginskienė E, et al. Mortality prediction in patients with acute kidney injury requiring renal replacement therapy after cardiac surgery. Medicina (Kaunas). 2017;53:217-23.
3. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. Ann Thorac Surg. 2012;93:337-47.
4. O'Neal JB, Shaw AD, Billings FT 4th. Acute kidney injury following cardiac surgery: current under-

standing and future directions. Crit Care. 2016;20: 187.
5. Durmaz I, Büket S, Atay Y, Yağdi T, Ozbaran M, Boğa M, et al. Cardiac surgery with cardiopulmonary bypass in patients with chronic renal failure. J Thorac Cardiovasc Surg. 1999;118:306-15.
6. Liu D, Liu B, Liang Z, Yang Z, Ma F, Yang Y, et al. Acute kidney injury following cardiopulmonary bypass: a challenging picture. Oxid Med Cell Longev. 2021;2021:8873581.
7. Kumar AB, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology. 2011;114:964-70.
8. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten SE. Effects of cardiopulmonary bypass on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. Anesthesiology. 2017;126:205-13.
9. Ortega-Loubon C, Fernández-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E. Cardiac surgery-associated acute kidney injury. Ann Card Anaesth. 2016;19:687-98.
10. Mao H, Katz N, Ariyanon W, Blanca-Martos L, Adýbelli Z, Giuliani A, et al. Cardiac surgery-associated acute kidney injury. Cardiorenal Med. 2013;3: 178-99.
11. Grünenfelder J, Zünd G, Schoeberlein A, Maly FE, Schurr U, Guntli S, et al. Modified ultrafiltration lowers adhesion molecule and cytokine levels after cardiopulmonary bypass without clinical relevance in adults. Eur J Cardiothorac Surg. 2000;17:77-83.
12. Kiziltepe U, Uysalel A, Corapcioglu T, Dalva K, Akan H, Akalin H. Effects of combined conventional and modified ultrafiltration in adult patients. Ann Thorac Surg. 2001;71:684-93.
13. Kuntz RA, Holt DW, Turner S, Stichka L, Thacker B. Effects of conventional ultrafiltration on renal performance during adult cardiopulmonary bypass procedures. J Extra Corpor Technol. 2006;38: 144-53.
14. Long DM, Jenkins E, Griffith K. Perfusionist techniques of reducing acute kidney injury following cardiopulmonary bypass: an evidence-based review. Perfusion. 2015;30:25-32.
15. Luciani GB, Menon T, Vecchi B, Auriemma S, Mazzucco A. Modified ultrafiltration reduces morbidity after adult cardiac operations: a prospective, randomized clinical trial. Circulation. 2001;104(12 Suppl 1):I253-9.
16. Foroughi M, Argani H, Hassntash SA, Hekmat M, Majidi M, Beheshti M, et al. Lack of renal protection of ultrafiltration during cardiac surgery: a randomized clinical trial. J Cardiovasc Surg (Torino). 2014;55:407-13.
17. Groom RC, Froebe S, Martin J, Manfra MJ, Cormack JE, Morse C, et al. Update on pediatric perfusion practice in North America: 2005 survey. J Extra Corpor Technol. 2005;37:343-50.
18. Paugh TA, Dickinson TA, Martin JR, Hanson EC, Fuller J, Heung M, et al. Impact of ultrafiltration on kidney injury after cardiac surgery: the michigan experience. Ann Thorac Surg. 2015;100:1683-8.
19. Oldeen ME, Angona RE, Hodge A, Klein T. American Society of ExtraCorporeal Technology: Development of Standards and Guidelines for Pediatric and Congenital Perfusion Practice (2019). J Extra Corpor Technol. 2020;52:319-26.
20. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clin Kidney J. 2013;6:8-14.
21. Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens FD. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. European Journal of Cardio-Thoracic Surgery. 2006;30:892-7.
22. Flythe JE, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. Semin Dial. 2011;24:259-65.
23. Bent P, Tan HK, Bellomo R, Buckmaster J, Doolan L, Hart G, et al. Early and intensive continuous hemofiltration for severe renal failure after cardiac surgery. Ann Thorac Surg. 2001;71:832-7.
24. Dehne MG, Sablotzki A, Mühling J, Dehne KL, Röhrig R, Hempelmann G. Renal effects of cardiopulmonary bypass in the elderly. Perfusion. 2002; 17:205-9.
25. Yi Q, Li K, Jian Z, Xiao Y-B, Chen L, Zhang Y, et al. Risk factors for acute kidney injury after cardiovascular surgery: evidence from 2,157 cases and 49,777 controls - a meta-analysis. Cardiorenal Medicine. 2016;6:237-50.

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Team Psychological Safety and Voice of Nurses in Affiliated Hospitals of Guangxi University of Chinese Medicine, the People's Republic of China

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ABSTRACT

OBJECTIVE To explore team psychological safety and voice of Chinese nurses and examine the relationship between team psychological safety and the voice of nurses in China.

METHODS A descriptive correlational study was conducted among 417 nurses who had worked at least one year in three affiliated hospitals of Guangxi University of Chinese Medicine, the People's Republic of China. Data was collected using a set of questionnaires consisting of Demographic Data Form, Team Psychological Safety Climate Scale (TPSCS), and Employee Voice Scale (EVS). The validity of the research instruments was tested by the original authors of the questionnaires. The Cronbach's alpha coefficients of the TPCSC and EVS were 0.96 and 0.91, respectively. Descriptive statistics and Spearman's Rank-order Correlation were used to analyze the data.

RESULTS The nurses perceived both team psychological safety and voice of nurses at a moderate level. Team psychological safety and voice had a strong positive correlation ($r = 0.51$, $p < 0.01$). The dimensions of speak one's mind freely, respect each other, interpersonal risk-taking, and mutual trust were found to be positively associated with voice ($r = 0.38$, $r = 0.48$, $r = 0.16$, and $r = 0.47$, $p < 0.01$, respectively).

CONCLUSIONS When nurses perceive psychological safety in their team, they are more likely to express ideas, information, opinions, and make cooperative contributions to the work unit and to the hospital. These findings can help guide hospitals and nursing administrators in developing strategies to improve team psychological safety which will lead to an increase in the voice of nurses.

KEYWORDS team psychological safety, voice, Chinese nurses

INTRODUCTION

Nurses constitute the majority of healthcare professionals and work closely with patients; they are responsible for observing and detecting early signs of unsafe conditions of patients (1). Having nurses be willing to speak up about behavior that violates safety rules and potential mistakes is essential to enhancing patient safety and quality of care as well as to preventing patient harm, e.g., medication errors, infection, and other sentinel events (2). It has been reported that most critical adverse events are the consequence of the failure of healthcare professionals to speak up, events which eventually result in harm to the patient (3). However, speaking up can be challenging for nurses. They may be reluctant to voice their opinions about work-related issues because they believe that open discussion or sharing their thoughts could adversely affect their position. They are concerned that they would appear to be a problematic person, or that their suggestions and

ideas would not result in any changes (4). Furthermore, when nurses are involved in adverse events, they become secondary victim and can become greatly affected by a series of psychological and psychosomatic symptoms such as anxiety, remorse, symptoms of depression, difficulty sleeping, and fear of future errors. If these feelings or symptoms are not properly addressed, they tend to negatively affect interpersonal relationships as well as the quality of communication in the workplace (5).

Furthermore, in a healthcare team, nurses' voice plays a significant role in improving team performance (6). Providing opportunities for nurses to share ideas and speak up about work-related concerns can increase their job satisfaction, reduce burnout rate, and thereby reduce the turnover of nurses (7). In recent years, nurses' voice has drawn extensive attention because of the benefits to patients, nurses, and the entire organization. Thus, encouraging nurses to express their voice in the organization is important and needs to be given more attention.

Voice is challenging-promotive extra-role behavior that is intended to improve the status quo (8). It could be future-oriented promotive expressions that aim at making innovative and constructive suggestions for change, or prohibitive expressions that focus on pointing out existing or potential harmful practices in the organization (9). In nursing, voice includes an array of behaviors in which nurses proactively speak up about concerns, report potential mistakes, and make suggestions related to patient safety and improving the workplace status quo (10). Nurses' voice has been studied in previous research; however, the findings have yielded different results. Studies conducted in the context of Chinese nursing have reported low to moderate levels of nurses' voice (11-13). The voice of nurses can be affected by various factors, e.g., personality (12), leadership behavior (14), and team psychological safety (15). Recent research has primarily explored associations between voice and individual differences or interpersonal factors, while rarely paying attention to the influence of psychological antecedents of promotive and prohibitive voice. Voice is intentional behavior. According to the theory of planned behavior, its occurrence may be contributed to by a variety of psychological antecedents (9).

Team psychological safety, defined as a shared belief in a team (16), allows members to express their thoughts freely, to have respect for each other's opinions and ways of doing things, to be able to speak up without worry about offending others or creating interpersonal issues and to have trust in other team members (17). Previous research on psychological safety has focused on exploration at the individual or organizational level. Psychological safety in the context of nursing should focus on the nursing team as the team members are influenced by the same set of team structures (16). In a psychologically safe team, nurses can effectively develop and maintain supportive and trusting interpersonal relationships. They are encouraged to proactively speak up about work-related concerns, to voice constructive suggestions, and to raise objections without fear of offending others (18). Most studies conducted in China on the levels of nurses' team psychological safety reported inconsistent findings, ranging from low to moderate (19-21). Extensive reviews of nursing research literature have shown that team psychological safety is important and has been found to be associated with the voice of nurses. To date, however, there have been no studies conducted on the nursing profession in China. There is a clear need to explore team psychological safety and voice and the relationship among nurses in China.

METHODS

Study design

A descriptive correlational study was conducted to determine the level of team psychological safety and voice among Chinese nurses and to explore the relationship between team psychological safety and voice.

Study setting, participants

The present study was conducted in three university hospitals in Guangxi Zhuang Autonomous Region, the People's Republic of China. The population of this study included 2,926 nurses who were currently working at affiliated

hospitals of the Guangxi University of Chinese Medicine. Yamane's formula (22) was used to calculate the sample size with a statistical significance level of .05. In consideration of the possible loss of participants, an additional 20% was added to the calculated sample size. A total of 422 questionnaires were distributed to nurses, of which 420 were returned. Of those, 417 completed questionnaires (99.29%) were included in the data analysis. We used a proportional stratified random sampling method to determine the number of participants from each department in the three hospitals. The participants were selected by a simple random sampling method from the list of names of nurses in each hospital. The inclusion criteria were: 1) nurses who had worked for their hospital for at least one year, and 2) nurses who worked in inpatient or outpatient departments and who provided direct nursing care to patients. The exclusion criteria were 1) individuals in the position of head nurse, nurse supervisor, or director of the nursing department, 2) nurses on maternity leave, sick leave, vacation, or continuing education, and 3) nurses who had participated in the reliability test.

Data collection

Data collection was done using a set of questionnaires consisting of three parts 1) the Demographic Data Form, developed by the researcher, which contained items about age, gender, marital status, educational level, working department, professional title, and working experience, 2) the Team Psychological Safety Climate Scale (TPSCS), developed by Wu and Chen (17), which consisted of 16 items and four dimensions: ability to speak one's mind freely, respect for each other, interpersonal risk-taking, and mutual trust (each dimension contained four items), and 3) the Employee Voice Scale (EVS), developed by Liang et al. (9), which consisted of 10 items and two dimensions: promotive voice (five items) and prohibitive voice (five items). All items of the TPSCS and EVS were rated on a five-point Likert scale ranging from 1 "strongly disagree" to 5 "strongly agree." The higher the score of both TPSCS and EVS, the higher level of nurses' team psychological safety and voice. The validity of the research instruments was tested by the original authors of those instruments. The reliability of both instruments was tested among 15 nurses in three hospitals. The Cronbach's alpha coefficient of the TPSCS was 0.96 and the dimensions of speak one's mind freely, respect each other, interpersonal risk-taking, and mutual trust were 0.93, 0.81, 0.93, and 0.83, respectively. The Cronbach's alpha coefficient of EVS was 0.91 and the dimensions of promotive voice and prohibitive voice were 0.75 and 0.89, respectively.

The data collection was conducted in March and April 2020. After obtaining permission for data collection, the researchers distributed the packages of questionnaires, including informed consent forms, to each participant. Research coordinators selected by the directors of the nursing departments were responsible for collecting the completed questionnaires in sealed envelopes and depositing them in designated boxes after two weeks and returning them to the researcher. The researcher checked the questionnaires for completeness before data analysis.

Data analysis

Data analysis was conducted using the Statistical Package for the Social Sciences Statistics (SPSS Statistics 23.0). Descriptive statistics (frequency, percentage, mean, standard deviation) were used to analyze demographic data and the team psychological safety and voice. Kolmogorov-Smirnov Z (KS) was used to test the data distribution. As the data distribution violated the assumption of normality, Spearman's rank correlation coefficient was used to analyze the correlation between variables. Based on Grove, Burns, and Gray (23), a positive value signified a direct correlation, a negative value indicated an inverse correlation. Correlation coefficient (r) values < 0.30 represented a weak correlation, 0.30 > r < 0.50 signified a moderate correlation, and r > 0.50 indicated a strong correlation. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

The research was approved by the Research Ethics Committee of the Faculty of Nursing, Chiang Mai University, Thailand (IRB certificate of approval number 013/2020). Permission for data collection was obtained from the directors

of the nursing departments in the three hospitals. All participants were given information and a thorough explanation of the study. They agreed to participate in this study and signed informed consent forms. Information regarding the participants was kept confidential and their identities were not disclosed. Only code numbers were used for questionnaire follow-ups.

RESULTS

As displayed in Table 1, the mean age of the participants was 30.79 (SD = 5.98), and most (60.43%) were between 22 and 30 years of age. Almost all the participants were female (97.60%), and most (60.19%) were married. A majority (71.22%) held a bachelor's degree in nursing, and 58.27% worked in a medical and surgical department. About half (53.72%) had obtained the professional title of Senior Nurse. Most of the participants (73.86%) had working experience of between 2 to 10 years, while the others had over 10 years' experience.

As shown in Table 2, nurses perceived the level of overall team psychological safety as moderate (mean = 3.47, SD = 0.49). The four dimensions, including speaking one's mind freely (mean = 3.41, SD = 0.56), interpersonal risk-taking (mean = 3.12, SD = 0.54), and mutual trust (mean = 3.57, SD = 0.67) were perceived as moderate, but the dimension of respect each

Table 1. Demographic characteristics of the participants (N = 417)

Demographic Characteristics	Frequency (n)	Percentage (%)
Age (years) (mean = 30.79, SD = 5.98, range = 22-58)		
22-30	252	60.43
31-40	134	32.13
41-50	27	6.48
>50	4	0.96
Gender		
Female	407	97.60
Male	10	2.40
Marital Status		
Married	251	60.19
Single	163	39.09
Divorced	3	0.72
Educational Level		
Diploma	2	0.48
Associate Degree	117	28.06
Bachelor Degree	297	71.22
Master Degree	1	0.24
Working Department		
Medical Department	153	36.69
Surgical Department	90	21.58
Outpatient Department	64	15.35
Operating Room	31	7.43
Obstetrics-Gynecology Department	30	7.19
Pediatrics Department	19	4.56
Intensive Care Unit	17	4.08
Emergency Room	13	3.12
Professional title		
Senior Nurse	224	53.72
Nurse-in-Charge	104	24.94
Junior Nurse	76	18.22
Associate Chief Nurse	11	2.64
Chief Nurse	2	0.48
Working Experience (mean = 8.65, SD = 6.62, range = 2-37)		
2-10	308	73.86
11-20	81	19.42
21-30	22	5.28
> 30	6	1.44

Table 2. Descriptive statistics for study variables (N = 417)

Variable	Mean	SD	Level
Team Psychological Safety			
Overall team psychological safety	3.47	0.49	Moderate
Speak one's mind freely	3.41	0.56	Moderate
Respect each other	3.77	0.75	High
Interpersonal risk-taking	3.12	0.54	Moderate
Mutual trust	3.57	0.67	Moderate
Voice			
Overall voice	3.66	0.51	Moderate
Promotive voice	3.81	0.59	High
Prohibitive voice	3.52	0.57	Moderate

other was perceived as high (mean = 3.77, SD = 0.75). The overall voice and the prohibitive voice as perceived by nurses were rated as moderate (mean = 3.66, SD = 0.51; mean = 3.52, SD = 0.57, respectively), while the promotive voice was rated as high (mean = 3.81, SD = 0.59).

As presented in Table 3, the results revealed a strong positive correlation between overall team psychological safety and voice (r = 0.51, p <.01). Additionally, the dimensions of speak one's mind freely, respect each other, interpersonal risk-taking, and mutual trust were significantly and positively associated with voice (r = 0.38, r = 0.48, r = 0.16, and r = 0.47, p < 0.01, respectively).

Table 3. Correlations among study variables (N = 417)

Team psychological safety	Voice
Overall	0.51**
Speak one's mind freely	0.38**
Respect each other	0.48**
Interpersonal risk-taking	0.16**
Mutual trust	0.47**

** p <.01

DISCUSSION

The results of the current study demonstrate that the nurses perceived team psychological safety at only a moderate level. This result is consistent with the results of Zou and Chen (21) and Yuan et al. (20), but not with the results of Yan and Kang (19) which reported a low level of team psychological safety. Some possible explanations for this divergence are explored below. First, the professional status of nursing may influence nurses' perception of team psychological safety. Healthcare exists as a well-entrenched status and hierarchical culture in which individuals with higher professionally-derived status seem to perceive a higher level of team psychological safety (24). In China, the professional status of nurses is generally reflected in the hierarchical division of the ladder of the nurse management system. Based on educational background, working experience, and work performance, nurses have been classified into five levels from novice to expert, namely, junior nurse, senior nurse, nurse-in-charge, associate chief nurse, and chief nurse (25). Promotion to each level involves correspondingly rigorous assessment and evaluation criteria. In a nursing team, nurses with higher professional status generally act as the backbone of the team. In addition to providing patient care services, they also assume responsibility for mentoring junior nurses, carrying out scientific research projects, and monitoring clinical nursing quality, and thus have more right to speak up than other members of the team. In the present study, 71.94% of the participants were in a relatively low professional status (junior nurses and senior nurses); only 3.12% were in a high professional status (associate chief nurses and chief nurses). Most of the nurses (308) had working experience of between 2-10 years and had developed teamwork to some degree, but not to the highest level. This could explain the moderate level of team psychological safety.

Second, the familiarity between team members may be an enabler of team psychological safety. Due to the interdependent nature of nursing work, nurses in a team usually com-

municate, collaborate, and share information with their team members in routine work face to face, which is bound to create familiarity among team members and to enhance their trust and tacit understanding of relationships (26). To some extent, the degree of cultivation of familiarity between team members is based on the level of stability of the team. When new members regularly join a team, team stability will be negatively affected and the building and maintenance of team psychological safety will become challenging (27). When nurses are employed by a hospital, they are assigned to different clinical nursing units according to each unit's workforce demand. To ensure the stability of the nursing team, nurses continue in their unit of initial assignment after that and are rarely transferred to other units. Our study found that the participants' average length of working with their current team was 8.65 years which indicates sufficient team composition stability to allow the team's psychological safety to develop.

Another finding of this study was that nurses perceived the overall voice as being at a moderate level. This is consistent with the results of Wang and Zu (11), while inconsistent with the result of a study conducted by Yi et al. (12) which reported a low level of nurses' voice. The first reason for this finding in the present study is related to organizational factors. The participants in this study were nurses working in tertiary hospitals. Compared to lower-level hospitals, tertiary hospitals pay more attention to the cultivation of nurses' voice, focusing more specifically and comprehensively on aspects of voice platform establishment, voice training project implementation, and environment creation (28). Hospital managers provide opportunities for nurses to voice their concerns through various channels, e.g., regular forums, seminars, quality control circles, questionnaires, and suggestion boxes, which are designed to encourage nurses to participate in the process of decision-making (29). Furthermore, the non-punitive system related to nurses reporting adverse events creates a psychologically secure environment that encourages nurses to proactively report patient safety issues. In practice, however, despite the establishment of a non-punishment nursing adverse events reporting system, the willingness of nurses to report adverse events appears to be lower than would be expected. The reason may be that the system is not fully implemented and/or that the name of the person reporting an event is not kept confidential (12).

Another reason for the relatively higher level of voice among tertiary hospital nurses may be related to demographic factors. In the current study, the mean period of work of the participants was 8.65 years, so they had accumulated a certain level of work experience through day-to-day practice, making it easier for them to detect work-related problems, raise constructive suggestions and brainstorm new ideas. As other studies have shown, the longer an employee works in their post, the greater the frequency of their voice (13). Another possible factor is education level. In this study, 71.22% of the nurses held a bachelor's degree compared to 42.1% of nurses in primary and secondary hospitals (28). That higher level of education makes the nurses more likely to participate in the operation and management of decision-making and to put forward viewpoints reflecting their values and using their influence (11). Another demographic factor that might have had a lowering effect on the voice of nurses was professional titles. Almost 70 percent of the nurses in this study were clinical nurses. In that capacity, they focus more on routine work than on proposing their ideas for preventing adverse events in their unit which may have led to the only moderate level of voice.

As anticipated, the results of this study suggest that team psychological safety is moderately positively associated with the voice of nurses. That is consistent with the results of a study conducted in the Netherlands by Alingh et al. (15), which indicated that when nurses feel psychologically safe in their team, they will more frequently speak up about patient safety issues. Voice is a discretionary and intentional behavior; due to the associated potential benefits and risks, individuals may consider in advance whether the consequences will be positive or negative before speaking up (30). Team psychological safety creates a favorable

context that allows individuals to evaluate the voice outcomes (31). In a psychologically safe environment, the team tolerates and encourages team members to express themselves frankly. Additionally, the team affords enough respect and trust to team members' suggestions and opinions, even if they hold objections. For that reason, team members are more willing to believe that it is safe for them to speak out without risk of possible punishment or of bringing about interpersonal risks when they voice challenges to the current status (32). In a healthcare team, for the team to work effectively, team members must accept and encourage diversity of opinions from others, respect and appreciate each other's roles, and respect each other's talents, beliefs, and professional contributions (33). When employees feel they are respected by others, they experience a psychological change of control beliefs (proactive motivation of "can-do") and a positive mood (proactive motivation of "energized-to") which then motivates voice (34). Healthcare team members openly discuss information, concerns, and opinions about safety-related issues through discretionary, change-oriented, and assertive communication which contributes to the prevention of adverse patient events (35). In summary, team psychological safety reduces concern that voice may lead to negative consequences and results in nurses being more confident and willing to use their voice in the team.

LIMITATIONS OF THE STUDY

This study was conducted in three university hospitals in China which are all tertiary public hospitals. Due to differences in organizational characteristics and structure, some of the study findings may not apply to other levels of hospitals or other types of healthcare organizations. Future research is needed to replicate this study in other levels of hospitals and other types of healthcare organizations in China. Additionally, qualitative and other types of research related to this topic are needed to explore the contributing factors for and barriers to voice among nurses in their workplace which could contribute to expanding insights relevant to the voice of nurses in the Chinese context.

CONCLUSIONS

To our knowledge, the present study is the first to explore the relationship between team psychological safety and voice in the context of Chinese nursing. The results highlight that both team psychological safety and voice of nurses need to be improved. The evidence to date regarding the benefits of team psychological safety and voice of nurses in healthcare suggests that further exploration is indispensable necessary to determine the identify enablers of these two variables. Additionally, the results expand understanding of the positive correlation between team psychological safety and voice, which provides basic information and has practical implications for nursing management in China. Interventions that facilitate nurses' team psychological safety should be implemented to motivate their voice in the workplace. For example, team leaders, as the anchors of the nursing team, could have dialogues that include deep listening, share their insights with team members, and avoid early evaluation to them overly hasty evaluation of new ideas and suggestions. Additionally, the team leader's leadership behavior was found to be an important influence on team psychological safety. Positive leadership behaviors, such as inclusiveness, trustworthiness, and ethical leadership, can facilitate team members' psychological safety (36). By contrast, if a leader behaves in an authoritarian or unsupportive manner or if they take a defensive stance, the feeling of psychological safety of team members will be diminished (24). Additionally, the non-judgmental listening of leaders can enhance nurses' team psychological safety (37). Establishing a foundation of open communication, mutual trust, and respect through team-based activities is needed to facilitate the psychological safety of nurses of different hierarchical status (38). Leaders who devote themselves to developing strategies and designing interventions, e.g., changing behaviors and providing support, are key to facilitating psychological safety in nursing teams.

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CONFLICTS OF INTEREST

None

REFERENCES

1. Okuyama A, Wagner C, Bijnen B. Speaking up for patient safety by hospital-based health care professionals: a literature review. BMC Health Serv Res. 2014;14:1-8.
2. Noort MC, Reader TW, Gillespie A. Speaking up to prevent harm: A systematic review of the safety voice literature. Saf Sci. 2019;117:375-87.
3. Weiss M, Kolbe M, Grote G, Spahn DR, Grande B. Why didn't you say something? Effects of after-event reviews on voice behaviour and hierarchy beliefs in multi-professional action teams. Eur J Work Organ Psychol. 2017;26:66-80.
4. Eriguc G, Ozer O, Turac İS, Songur C. Organizational silence among nurses: a study of structural equation modeling. Int J Bus Humanit Technol. 2014;4:150-62.
5. Busch IM, Moretti F, Purgato M, Barbui C, Wu AW, Rimondini M. Psychological and Psychosomatic Symptoms of Second Victims of Adverse Events: a Systematic Review and Meta-Analysis. J Patient Saf. 2020;16:e61-e74.
6. Krenz H, Burtscher MJ, Grande B, Kolbe M. Nurses' voice: the role of hierarchy and leadership. Leadersh Health Serv. 2020;33:12-26.
7. Holland PJ, Allen BC, Cooper BK. Reducing burnout in Australian nurses: The role of employee direct voice and managerial responsiveness. Int J Hum Resour Manag. 2013;24:3146-62.
8. Van Dyne L, LePine JA. Helping and voice extra-role behaviors: Evidence of construct and predictive validity. Acad Manag J. 1998;41:108-19.
9. Liang J, Farh CI, Farh JL. Psychological antecedents of promotive and prohibitive voice: A two-wave examination. Acad Manag J. 2012;55:71-92.
10. Mannion R, Davies HT. Cultures of silence and cultures of voice: the role of whistleblowing in healthcare organisations. Int J Health Policy Manag. 2015;4:503.
11. Wang YP, Zu XJ. Influence of voice behavior and core self-evaluation on career growth among emergency nurses. J Nurs Sci. 2018;33:63-7. [Chinese]
12. Yi KG, Ding SQ, Liu ZN, Xie JF, Qin CX, Zheng F, et al. Study of the correlationship between nurses' voice behavior and proactive personality. Nurs J Chin PLA. 2016;33:1-6. [Chinese]
13. Zhao SL, Yang QF, Yang Q. Influence of organizational climate on the voice behavior of nursing staff in operating room. Hosp Manag Forum. 2018;35:70-3. [Chinese]
14. Erkutlu H, Chafra J. Leader's integrity and employee silence in healthcare organizations. Leadersh Health Serv (Bradf Engl). 2019;32:419-34.
15. Alingh CW, van Wijngaarden JD, van de Voorde K, Paauwe J, Huijsman R. Speaking up about patient safety concerns: The influence of safety management approaches and climate on nurses' willingness to speak up. BMJ Qual Saf. 2019;28:39-48.
16. Edmondson AC. Psychological safety and learning behavior in work teams. Adm Sci Q. 1999;44:350-83.
17. Wu ZP, Chen FT. [The scale development of team psychological safety climate in the Chinese cultural context]. Chin J Manag. 2011;8:73-80. [Chinese]
18. Pfeifer LE, Vessey JA. Psychological safety on the healthcare team. Nurs Manage. 2019;50:32-8.
19. Yan MQ, Kang L. [Relationship between team psychological safety climate and occupational coping self-efficacy among clinical nurses]. J Nurs Sci, 2017;33:59-61. [Chinese]
20. Yuan XL, Zhang HZ, Zhou MF. [Correlation study on team psychological safety and resilience of medical staff]. Hosp Manag Forum. 2017;34:63-6. [Chinese]
21. Zou ZZ, Chen S. [Effect of team psychological safety on perceptions of benefits of nurses from operating room]. Hosp Manag Forum. 2016;33:53-6. [Chinese]
22. Yamane T. Statistics: An introductory analysis. New York: Harper & Row; 1973.
23. Grove SK, Burns N, Gray J. The practice of nursing research: Appraisal, synthesis, and generation of evidence. St. Louis: Elsevier Health Sciences; 2012.
24. Nembhard IM, Edmondson AC. Making it safe: The effects of leader inclusiveness and professional status on psychological safety and improvement efforts in health care teams. J Organ Behav. 2006;27:941-66.
25. Shi YL, Li JP. Research progress of hierarchical division in nursing ladder management in China. Chin Nurs Res. 2016;3:109-12.
26. O'Donovan R, McAuliffe E. A systematic review exploring the content and outcomes of interventions to improve psychological safety, speaking up and voice behaviour. BMC Health Serv Res. 2020;20:101.
27. O'Leary DF. Exploring the importance of team psychological safety in the development of two interprofessional teams. J Interprof Care. 2016;30:29-34.
28. Chen F, Wan K, Hu YQ, Zuo B, Wang DH. [Study on the current situation and influencing factors of nurses' voice behavior in 2A-level hospitals]. J Nurs Adm. 2020;20:131-4. [Chinese]
29. Huang S, He Y, Zhou H, Zhang L. [Impact of leader rapport management on organizational trust and voice behavior of nursing staff]. J Nurs Sci. 2016;31:51-3. [Chinese]
30. Liu W, Zhu R, Yang Y. I warn you because I like you: Voice behavior, employee identifications,

and transformational leadership. Leadersh Q. 2010;21:189-202.
31. Bienefeld N, Grote G. Speaking up in ad hoc multiteam systems: Individual-level effects of psychological safety, status, and leadership within and across teams. Eur J Work Organ Psychol. 2014;23:930-45.
32. Miao R, Lu L, Cao Y, Du Q. The high-performance work system, employee voice, and innovative behavior: The moderating role of psychological safety. Int J Environ Res Public Health. 2020;17:1150.
33. Babiker A, El Husseini M, Al Nemri A, Al Frayh A, Al Juryyan N, Faki MO, Assiri A, Al Saadi M, Shaikh F, Al Zamil F. Health care professional development: Working as a team to improve patient care. Sudan J Paediatr. 2014;14:9.
34. Ng TW, Hsu DY, Parker SK. Received respect and constructive voice: The roles of proactive motivation and perspective taking. J Manag. 2019; 0149206319834660.
35. Lee SE, Choi J, Lee H, Sang S, Lee H, Hong HC. Factors influencing nurses' willingness to speak up regarding patient safety in East Asia: A systematic review. Risk Manag Healthc Policy. 2021;14:1053.
36. Aranzamendez G, James D, Toms R. Finding antecedents of psychological safety: A step toward quality improvement. Nurs Forum (Auckl). 2015;50:171-8.
37. Cave D, Pearson H, Whitehead P, Rahim-Jamal S. CENTRE: creating psychological safety in groups. Clin Teach. 2016;13:427-31.
38. Campbell AR, Layne D, Scott E, Wei H. Interventions to promote teamwork, delegation and communication among registered nurses and nursing assistants: An integrative review. J Nurs Manag. 2020;28:1465-72.

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Case Report **Open Access**

Elevated INR Following Coadministration of Warfarin with Fenofibrate: A Case Report and Review of the Literature

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ABSTRACT

Fenofibrate, a lipid lowering drug, can increase the effects of warfarin and may cause bleeding more easily. We report a case of a 58-year-old Thai male patient who was administered warfarin at 27 mg per week to achieve the target international normalized ratio (INR) value. Fenofibrate at 200 mg per day was coadministered with warfarin for three months. The patient's INR value increased to 5.38, but he did not experience any abnormal bleeding. His compliance with the medication regime was good, and he denied using other medications or herbal and dietary supplements. Warfarin was subsequently withheld for three days then resumed at the same dose after the INR value had returned to the normal range. Concurrently, fenofibrate was discontinued because his triglyceride level declined to below the normal target. One week later, his INR value had decreased to 2.44. This case presents an increased INR value when fenofibrate was concomitantly used with warfarin. This occurs because fenofibrate inhibits the CYP2C9 enzyme and displaces the protein albumin, thereby increasing the effect of warfarin. These results are consistent with several other case reports. The onset of this effect occurs approximately one week to one month after initiating fenofibrate . Healthcare professionals should carefully monitor INR values to ensure safe and efficacious management in patients using both warfarin and fenofibrate.

KEYWORDS warfarin, fenofibrate, drug interaction

INTRODUCTION

Warfarin is an oral anticoagulant used to prevent thromboembolism in patients with atrial fibrillation (AF), pulmonary embolism (PE), deep vein thrombosis (DVT), and mechanical valve replacement (1). Warfarin is completely absorbed and highly protein binding by approximately 100% (1,2). Warfarin is metabolized in the liver. The racemic warfarin mixture includes two optically active isomers, R and S which are differentially metabolized by cytochrome P450 (CYP450) isozymes. S-warfarin is primarily metabolized by CYP2C9 and CYP3A4, while CYP1A2 and CYP3A4 are important metabolizers of R-warfarin (1). R-warfarin has a longer half-life than S-warfarin, 45 hours vs. 29 hours, but, S-warfarin is approximately three time more potent as a blood anticoagulant than R-warfarin (3,4).

One major problem with warfarin use is the occurrence of drug-drug or drug-herb interaction, which can be particularly problematic in ischemic and bleeding patients. Warfarin use in combination with fenofibrate occurs practically. Fenofibrate, a fibric acid derivative, has long been the main therapy for treating hypertriglyceridemia (5). Fenofibrate is metabolized mainly by CYP2C9 and has high protein binding, similar to warfarin, which is why combining warfarin with fenofibrate can cause

increased international normalized ratio (INR) values above the normal range. Previous drug-drug interaction studies have shown that fenofibrate use is associated with elevated INR values and/or bleeding risk, especially in patients receiving high doses of fenofibrate (6-9). Thus, it is important to closely monitor INR values when warfarin and fenofibrate are taken together (4,10,11). This case report aimed to explain the effects of fenofibrate on warfarin. The results of this study may be useful for appropriate management and INR monitoring in patients receiving both warfarin and fenofibrate.

CASE REPORT

A 58-year-old Thai male had hypertension, gout, type 2 diabetes mellitus (DM), AF, mechanical valve replacement at the mitral position and had an ischemic stroke. He had been taking the following medications at the same doses for six months: atenolol 100 mg/day, allopurinol 300 mg/day, colchicine 0.6 mg/day, alogliptin 25 mg/day, metformin 2,000 mg/day, omeprazole 20 mg/day, and warfarin 27 mg/week. He denied smoking and consumption of alcohol. For a visit at the cardiology outpatient department, his vital signs and physical examination results were normal. However, during the past 5 months, his INR values had increased from 2.55 to 5.28 without any signs of bleeding, but he did not have any bleeding. His previous INR value while taking 27 mg/week of warfarin was within the target range of 2.5-3.5. The supratherapeutic INR value of 5.28 could not be explained by other causes such as lack of compliance with the prescribed medicine regime, diseases (e.g., heart failure, hypoalbuminemia, hyperthyroidism or weight loss), vegetable consumption, or herbal supplement intake. The pharmacist reviewed the medication profile and found that he had received fenofibrate from another hospital for the management of hypertriglyceridemia resulting in the co-medication of fenofibrate 200 mg once daily and warfarin for three months. A drug-drug interaction may have been the cause of the INR value being greater than the therapeutic range. The physician decided to withhold warfarin for three days, then prescribed the same dose of warfarin (27 mg/week) to be resumed. Fenofibrate was discontinued because the triglyceride level had reached the normal range and the patient agreed to observe diet control. One week later, his INR value had decreased to 2.44.

DISCUSSION

Fenofibrate inhibits the activity of CYP2C9 isozyme, including the competitive protein binding of warfarin. Warfarin is a substrate of CYP2C9, especially the S-isomer warfarin which is more potent than the R-isomer warfarin (1,12). For that reason, concomitant use of fenofibrate and warfarin can cause supratherapeutic INR values and/or bleeding symptoms. Several studies have reported the effect of warfarin interaction with fenofibrate. In 1998, Kathyrn et al. (8) reported two patients who received warfarin concomitant with fenofibrate. The first case involved a 47-year-old man who received warfarin at 12.5-15 mg/day to prevent thromboembolism from AF. His INR remained in the therapeutic range (2.0-3.0) for 20 weeks. Then fenofibrate 200 mg/day was initiated to reduce his triglyceride levels. A week later, he had flank pain symptoms and tea-colored urine. Urinary analysis showed red blood cells and his INR value had increased to 8.5. Warfarin and fenofibrate were discontinued and a vitamin K injection of 10 mg was administered. Two days later, the INR value had returned to the normal range. The second case involved a 53-year-old man who had undergone mechanical heart valve surgery at the aortic valve position due to ischemic heart disease (IHD) and dyslipidemia. He received warfarin 5 mg/day and his INR value was controlled within the therapeutic ranged (2.8-3.5) for six weeks. At that time, fenofibrate was started with warfarin for 10 days. Subsequently, the INR value increased from 2.8-3.5 to 5.6. The patient followed the dosage instructions and had no history of other drug use. Physical examination did not indicate heart failure, and liver function was normal. The physician stopped the administration of fenofibrate, after which the INR value returned to normal. Another case report by Kim and Mancano (13) described drug-drug interactions in two female patients aged 71 years and 80 years old who had received

the same dose of warfarin. Their INR values were kept within the target range. Both patients took the medications as directed and at similar doses. Thyroid function and liver function tests were normal. The addition of fenofibrate in the two patients together with the same therapeutic doses of warfarin increased the anticoagulant effect. The INR values of both patients increased three-fold and two-fold from the baseline INR values, respectively. However, no bleeding disorders were identified. The physician then reduced the warfarin dosage by approximately 30-40%. This case is consistent with a case report by Breault et al. (14) where a 28-year-old male patient was administered warfarin to prevent development of thromboembolic events. He had previously undergone Mustard procedure surgery and had underlying diseases including heart failure, dyslipidemia and gout. He was prescribed colchicine 0.6 mg/day, allopurinol 300 mg/day, furosemide 40 mg/day, ramipril 10 mg/day, metoprolol 50 mg twice daily, and warfarin 24-25 mg/week. The INR value was reduced and remained in the therapeutic range (INR 2.5) for 15 months. However, after initiating fenofibrate 200 mg once daily, the INR value increased to 5.48. The physician then decided to decrease the dose of warfarin by approximately 30%. One week later, the INR value had turned to the normal range. Characteristics of case reports on the concomitant use of warfarin and fenofibrate are shown in Table 1. The cohort study by Leonard et al. provides evidence that the concomitant use of antihyperlipidemics, including fenofibrate, together with warfarin can increase the risk of gastrointestinal bleeding and intracerebral hemorrhage (7). In addition, Polnak et al. reported the influence of fibrate on warfarin dose and INR values in patients receiving chronic warfarin therapy. In that retrospective, pre-to-post study, 197 patients used fenofibrate and 124 patients used gemfibrozil. The results showed the increased

Table 1. Characteristics of case reports on the concomitant use of warfarin and fenofibrate

Case studies/ reports	Case description; baseline warfarin dose	Duration of concomitant drug	Increase in INR level	Management	Comments
Ascah KJ, et al. (8)	47-year-old man; 12.5-15 mg/day	1 week	> 8.5	Discontinued warfarin and fenofibrate	Closely monitoring the INR level and observe for any sign of bleeding
		13 days	5	Reduced warfarin dose by 27%-29%	
	56-year-old man; 35 mg/week	10 days	5.6	Discontinue warfarin and fenofibrate	
Aldridge MA, et al. (15)	79-year-old man; 42 mg/week	4 weeks	18	Discontinued warfarin and fenofibrate	Closely monitoring the INR level and observe for any sign of bleeding
Kim KY, et al. (13)	71-year-old woman; 23 mg/week	15 days	6.7	Reduced warfarin dose by 37%-41%	Closely monitoring the INR level and reduce by 20% the warfarin dose before restarting therapy
	80-year-old woman; 20 mg/week	3 weeks	4.6	Reduced warfarin dose by 35%	
Breault RR, et al. (14)	28-year-old man; 24-25 mg/week	1 week	1.9	Reduced warfarin dose by 32%	Closely monitoring the INR level
This case report	58-year-old man; 27 mg/week	3 months	5.28	Discontinued warfarin and fenofibrate for three days Restarted warfarin at the same dose (27 mg/week)	Closely monitoring the INR level

INR values after starting fenofibrate were not statistically significant (6).

In the present case report, the interaction between warfarin and fenofibrate was shown to elevate the INR value. This association has been demonstrated in previous case reports. However, the present case is different from previously reported cases in that the onset of the effect from the concomitant use of warfarin and fenofibrate occurred 90 days after initiating fenofibrate whereas in the other case reports the range of time to onset of the effect was between one week and one month (8,13,15). The conclusion from published reports as well as this study is that warfarin should be discontinued and only reinitiated if the INR value returns to the normal therapeutic range. This drug-drug interaction requires careful adjustment of the warfarin dose, e.g., decreasing the warfarin dose by 20-35% from the initial regimen. Healthcare professionals should carefully monitor INR values of patients with warfarin-fenofibrate to ensure efficacious and safe treatment, especially for patients who have a high risk of bleeding.

REFERENCES

1. Wittkowsky AK. Warfarin and other coumarin derivatives: pharmacokinetics, pharmacodynamics, and drug interactions. Semin Vasc Med. 2003;3: 221-30.
2. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:204s-33s.
3. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol. 1998;45:525-38.
4. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:160s- 98s.
5. Balfour JA, McTavish D, Heel RC. Fenofibrate. Drugs. 1990;40:260-90.
6. Polnak JF, Delate T, Clark NP. The influence of fibrate initiation on INR and warfarin dose in patients receiving chronic warfarin therapy. J Thromb Thrombolysis. 2018;46:264-70.
7. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, et al. Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics. Int J Cardiol Heart Vasc. 2017;228:761-70.
8. Ascah KJ, Rock GA, Wells PS. Interaction between fenofibrate and warfarin. Ann Pharmacother. 1998;32:765-8.
9. Guo C, Xue S, Zheng X, Lu Y, Zhao D, Chen X, et al. The effect of fenofibric acid on the pharmacokinetics and pharmacodynamics of warfarin in rats. Xenobiotica. 2018;48:400-6.
10. El-Helou N, Al-Hajje A, Ajrouche R, Awada S, Rachidi S, Zein S, et al. Adverse drug events associated with vitamin K antagonists: factors of therapeutic imbalance. Vasc Health Risk Manag. 2013;9: 81-8.
11. Juurlink DN. Drug interactions with warfarin: what clinicians need to know. CMAJ. 2007;177:369-71.
12. Balfour JA, McTavish D, Heel RC. Fenofibrate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. Drugs. 1990;40:260-90.
13. Kim KY, Mancano MA. Fenofibrate potentiates warfarin effects. Ann Pharmacother. 2003;37:212-5.
14. Breault R, Klakowicz A, George-Phillips K, Bungard T. Warfarin dosing after initiation of fenofibrate. Can J Hosp Pharm. 2005;58.
15. Aldridge MA, Ito MK. Fenofibrate and Warfarin Interaction. Pharmacotherapy. 2001;21:886-9.