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Original Article

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Comparison of Blood and Urinary Cannabis Profiles Between Road Traffic Injury (RTI) and Other Causes of Death in Thai Postmortem Cases

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ABSTRACT

OBJECTIVE This study aims to compare blood and urinary cannabis profiles between road traffic injury (RTI) and other unnatural causes of death in the Thai population.

METHODS A cross-sectional study was conducted of Thai postmortem cases where the individual who died was 15 years old or over. Sex, age, cause of death, manner of death, blood alcohol concentration (BAC), and concomitant drugs found were documented for each case. Blood and urinary concentrations of delta9-tetrahydrocannabinol (THC) and its two metabolites, 11-hydroxy-delta9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-delta9-tetrahydrocannabinol (THC-COOH), were analyzed using gas chromatography tandem mass spectrometry (GC-MS/MS). Statistical analysis was performed using the Mann-Whitney U test and Kruskal-Wallis H test.

RESULTS A total of 80 subjects were included in this study, comprising 43 RTI and 37 non-RTI subjects. All the RTI cases were motorcycle riders. Blood concentrations of THC, 11-OH-THC, and THC-COOH in the RTI group were significantly higher than those in the non-RTI group ($p < 0.01$). The number of subjects who had recent cannabis exposure in the RTI group was significantly higher than in the non-RTI group ($p< 0.05$). Furthermore, the blood concentrations of THC, 11-OH-THC, and THC-COOH in subjects who used cannabis without other drugs of abuse or medications were significantly higher than those in subjects who used cannabis with other drugs of abuse or other medications ($p < 0.05$).

CONCLUSIONS Blood THC, 11-OH-THC, and THC-COOH concentrations in RTI cases were significantly higher than in cases with other unnatural causes of death.

KEYWORDS cannabis, road traffic injury (RTI), motorcycle rider, Thai

INTRODUCTION

Cannabis is one of the most common drugs of abuse used by adolescents and adults worldwide. According to figures from the United States (US), an estimated 48 million people 12 years old or over had experience of cannabis use in 2019 (1). In 2019 the Thai government initiated a public policy to authorize cannabis use for medical purposes and has allowed cannabis use at home as well as cannabis home cultivation since 2022 (2). A previous study in Thailand suggested that the prevalence of lifetime cannabis use in Thai

people in 2011 was 5.05%, while the prevalence of cannabis use in the previous year was 0.20% (3). Subsequently, following amendments to government policy related to cannabis, the number of users has risen, with a recent study reporting that approximately 15.00% of Thai people had used cannabis (around 7.5 million people 20 years old or over) (4). In addition, a 2024 study focusing on chronic pain patients found that the prevalence of active cannabis use was 15.00% in chronic cancer pain cases and 3.10% in non-cancer pain cases (5). Moreover, the prevalence of cannabis use in Thai people who were 18-65 years old has also increased, from about 4.00% in 2021 to about 25.00% in 2022 (2). These figures suggest that the current trend of cannabis use in Thailand is increasing.

Cannabis contains an important psychoactive substance called delta9-tetrahydrocannabinol (THC). When THC enters the bloodstream, it is metabolized into two main metabolites: 11-hydroxy-delta9-tetrahydrocannabinol (11-OH-THC) and 11-Nor-9-carboxy-delta9-tetrahydrocannabinol (THC-COOH) (6). The presence of blood THC concentrations greater than 2-3 ng/mL and a ratio of THC-COOH/THC > 1 suggests recent cannabis exposure (within the past 6-8 hours) (6). Additionally, it has been suggested that chronic cannabis users could have residual blood THC concentrations of <2 ng/mL at 12 hours after cannabis use (6). The presence of THC and/or 11-OH-THC in blood and/or urine could also be used as a marker of recent cannabis use (6). Thus, the concentrations of THC, 11-OH-THC, and THC-COOH in blood and urine are important for estimating the time of cannabis exposure, where confirmation of such exposure could be used for implying clinical impairment.

According to legislation in the US, Canada, and the United Kingdom (UK), THC concentrations of 2 to 5 ng/mL are used to indicate driving under the influence of cannabis (7). A previous study found that the mean and median whole blood THC concentrations in all drivers arrested for driving under the influence of drugs (DUID) were 4.9 and 3 ng/mL, respectively, while the mean and median whole blood THC concentrations in all drivers who died while driving with cannabis in their postmortem blood were 11.7 and 4.5 ng/mL, respectively (8). That study suggested that most DUID cases were recent cannabis users, and reported that the whole blood THC concentrations in postmortem cases were higher than those in drivers arrested for DUID (8). Another study found that the majority of motorists tested who were suspected of DUID had whole blood THC concentrations between 1-6 ng/mL. This finding also suggests that most of the drivers had recently used cannabis (9).

Currently, there is still a lack of information about the cannabis concentration profiles in Thai people. Consequently, the present study aimed to investigate the concentration profiles of THC, 11-OH-THC, and THC-COOH in blood and urine samples obtained from road traffic injury (RTI) cases, focusing on motorcycle riders, who comprise the majority of RTI cases in Thailand, and comparing that with samples obtained from Thai people who had other unnatural causes of death. This information was collected to elucidate the levels of cannabis exposure in these two groups. It is expected that the study findings and data will be useful for further research on cannabis exposure in the Thai population.

METHODS

Study design and data collection

A cross-sectional study was conducted of medico-legal cases sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University. Thai postmortem cases that were at least 15 years old at the time of death and which had been sent for autopsy between May 1, and October 31, 2024, were recruited. Individuals who were dead at the scene and who had undergone the autopsy procedure within 24 hours after death were included. All cases that were positive for THC and/or its two metabolites in either blood or urine were included. The exclusion criteria were decomposed bodies and bodies with extensive injuries, such as injuries from being run over by a motor vehicle. All cases that were suspected of being cannabis-related sudden cardiac death or cannabis intoxication were excluded.

This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University (COA No. Si 937/2023, SIRB protocol No. 910/2566 (IRB2)).

Chemicals and reagents

THC, 11-OH-THC, and THC-COOH at a concentration of 1 mg/mL were purchased from LGC (LGC Standards, Teddington, England) and THC-COOH-d3 at a concentration of 100 µg/mL was also sourced from LGC. LC-MS-grade methanol, acetonitrile, ethyl acetate, and n-hexane were acquired from Duksan Pure Chemicals Co., Ltd. (Gyeonggi-do, South Korea.) Acetic acid was purchased from vWR, Radnor, PA, USA. N, O-bis (trimethylsilyl) trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane (TMCS) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Solid phase extraction (SPE) Oasis® MAX cartridges (60 mg, 3 mL) were obtained from Waters (Waters Oasis, Wexford, Ireland). All other chemicals and reagents were provided by U&V Holding (Thailand) Co., Ltd., Nonthaburi, Thailand. The deionized water (dH_2O) used in this study was produced using a Merck Millipore Direct-Q® 3 UV-R Water Purification System (Burlington, MA, USA).

Instrumentation

Gas chromatography-triple quadrupole tandem mass spectrometry (GC-MS/MS) was performed using a Thermo Scientific™ TSQ™ 9000 Triple Quadrupole GC-MS/MS system (Waltham, MA, USA), with the GC utilizing an HP5-MS (30 m × 0.25 mm ID coated with a 0.25 µm film) capillary column. The GC conditions were set according to the temperature program. The initial temperature was 150°C, for 3 minutes, then the temperature was elevated to 220°C at a rate of 40°C/minute, followed by an increase to 300°C at a rate of 7°C/minute and then holding there for 5 minutes. Helium was used as the carrier gas at a flow rate of 1.3 mL/minute. The injector and transfer line temperatures were set at 150°C and 250°C, respectively. The mass analyzer was operated in the electron ionization mode at 70 eV and the ion source temperature was programmed at 230°C. The selected reaction monitoring (SRM) mode was applied, as described in Table 1.

Sample preparation and extraction procedure

Blood samples were collected from the femoral vein, while urine samples were aspirated from the urinary bladder during the autopsy for collection. Then, 10 mL of blood was put into a red-capped blood tube while 30 mL of urine was put into a plastic bottle. All the blood and urine samples were stored at 4°C in the laboratory and then analyzed for THC and its metabolites the next day by GC-MS/MS.

Solid phase extraction (SPE) was achieved using Waters Oasis® MAX cartridges (60 mg, 3 mL) (Waters Oasis, Wexford, Ireland). The SPE cartridges were preconditioned with methanol and dH_2O. Then, the prepared samples was loaded into the cartridges. Next, a washing step was performed with 2 mL of 50% methanol followed by 2 mL of n-hexane. After drying the SPE cartridges for 5 minutes, the target analytes were eluted using 2 mL of an elution solvent mixture (49% n-hexane: 49% ethyl acetate: 2% acetic acid). Then the eluent was dried under a nitrogen stream at 40°C. Next, the derivatization process was performed by adding 50 µL of BSTFA containing 1% TMCS into the residue. The incubation process was performed at 70°C for 40 minutes, then the cartridges were left to cool at room temperature at the end of the process of derivatization. Finally, the derivatized product was injected into a GC-MS/MS system for analysis.

Method validation

Method validation was conducted following the Standard Guidelines in Forensic Toxicology (10). The expired whole blood used in the method validation for blood was obtained from the Department of Transfusion Medicine, Siriraj Hospital,

Table 1. Selected reaction monitoring (SRM) mode for THC and its metabolites

Analytes	Quantifier ion	Qualifier ion 1	Qualifier ion 2	Collision energy (eV)	Retention time (min)
THC	371.2 > 289.2	371.2 > 305.2	371.2 > 265.2	15 > 10 > 10	10.04
11-OH-THC	371.2 > 289.2	371.2 > 305.2	371.2 > 265.2	15 > 10 > 10	12.20
THC-COOH	371.2 > 289.2	371.2 > 305.2	371.2 > 265.2	15 > 10 > 10	13.62
THC-COOH-d_3	374.3 > 292.2	374.3 > 308.2	374.3 > 268.2	15 > 10 > 10	13.60

THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta9-tetrahydrocannabinol

Mahidol University, while synthetic urine was used for the method validation for urine. A complete chromatographic separation of THC and its metabolites from the endogenous baseline noise was carried out during the interference studies. In addition, other drugs of abuse, including methamphetamine, amphetamine, 3,4-methylenedioxy methamphetamine (MDMA), 3,4-methylenedioxy amphetamine (MDA), cocaine, benzoylecgonine, 6-acetylmorphine, codeine, morphine, fentanyl, methadone, tramadol, ketamine, mitragynine, lysergic acid diethylamide (LSD), phencyclidine (PCP), and psilocybin were tested to ascertain whether they would interfere with the target analysis during the THC analysis. The limit of detection (LOD) and lower limit of quantitation (LLOQ) were evaluated for THC, 11-OH-THC, and THC-COOH in both the blood and urine samples. Finally, the LOD and LLOQ for combined THC, 11-OH-THC, and THC-COOH were set at 0.1 and 0.2 ng/mL, respectively.

The linearity ranges for THC, 11-OH-THC, and THC-COOH in the blood and urine samples were obtained at concentrations of 0.2, 0.5, 1, 2, 5, 10, and 20 ng/mL. Calibration curves for THC, 11-OH-THC, and THC-COOH were obtained using Thermo ScientificTM (Waltham, MA, USA) TraceFinderTM 5.0 SP1 Software®. For the linearity range criteria, a coefficient of determination (r2) ≥ 0.99, an accuracy of each calibrator within ±15% (LLOQ ± 20%), and a % coefficient of variation (%CV) ≤ 15% were achieved. A summary of the criteria of the linearity ranges for THC and its two metabolites in blood and urine in this study is shown in Table 2.

Accuracy and precision were evaluated for the spiked blood and urine samples at three quality control (QC) concentrations, 0.6, 6, and 15 ng/mL. The accuracy of each QC concentration should be within ± 15% and the precision evaluated by the %CV should also be ≤ 15%. The obtained accuracy and precision of these three concentrations of THC, 11-OH-THC, and THC-COOH in blood and urine are shown in Table 3 and Table 4, respectively. Moreover, the dilution integrity was evaluated for a dilution factor of 1:5 for THC and THC-COOH and 1:50 for THC-COOH due to the high concentrations of THC-COOH in the authentic samples. Accuracy and precision testing was also performed and all the results, both in the blood and urine samples, passed the criteria of acceptability of an accuracy within ± 15% and precision evaluated by a %CV ≤ 15%.

Statistical analysis

Statistical analysis was conducted using IBM SPSS® Statistics for Windows version 25. Descriptive statistics, including the mean, median, and standard deviation (SD), were calculated. The Kolgomorov-Smirnov test was used for normality testing of the blood and urinary profiles of cannabis and its metabolites. It was found that the blood and urinary cannabis and its metabolites were not normally distributed. Thus, comparisons of the blood and urinary concentrations of cannabis and its metabolites were performed using the Mann-Whitney U test and Kruskal-Wallis H test where appropriate. Contingency table chi-square analysis was used for comparison of the number of subjects between the recent and non-recent cannabis exposure cases and for comparison of the number of subjects who had used other drugs with cannabis in the RTI and non-RTI groups, respectively.

Table 2. Summary of the linearity ranges for THC, 11-OH-THC, and THC-COOH in blood and urine

Analyte	Range (ng/mL)	Linear regression equation		r^2
		Slope	Intercept	
Blood				
THC	0.2-20	0.047998	+0.017198	≥0.99
11-OH-THC	0.2-20	0.030840	+0.026120	≥0.99
THC-COOH	0.2-20	0.012535	+0.075585	≥0.99
Urine				
THC	0.2-20	0.032106	+0.016848	≥0.99
11-OH-THC	0.2-20	0.033484	+0.054792	≥0.99
THC-COOH	0.2-20	0.013934	+0.030306	≥0.99

THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta9-tetrahydrocannabinol

Table 3. Accuracy and precision of three QC concentrations in blood samples

QC concentration (ng/mL)	Accuracy (%) (n=5)	Precision (n=5)	
		Intra-day (%)	Inter-day (%)
THC			
0.6	90.33-111.67	≤12.47	≤11.67
6	89.17-112.67	≤12.58	≤11.84
15	86.67-110.33	≤11.33	≤10.18
11-OH-THC			
0.6	88.33-113.67	≤12.74	≤13.63
6	87.67-112.17	≤13.62	≤12.37
15	90.58-113.83	≤11.81	≤12.53
THC-COOH			
0.6	89.33-112.33	≤11.67	≤13.05
6	87.17-111.33	≤11.94	≤12.83
15	88.58-113.08	≤10.42	≤13.17

THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta9-tetrahydrocannabinol

Table 4. Accuracy and precision of three QC concentrations in urine samples

QC concentration (ng/mL)	Accuracy (%) (n=5)	Precision (n=5)	
		Intra-day (%)	Inter-day (%)
THC			
0.6	87.67-113.33	≤13.67	≤12.85
6	91.83-114.33	≤13.58	≤11.45
15	91.67-113.42	≤10.17	≤9.64
11-OH-THC			
0.6	86.33-112.33	≤13.33	≤12.57
6	88.83-113.17	≤12.17	≤12.47
15	93.58-109.08	≤10.08	≤11.64
THC-COOH			
0.6	88.33-111.33	≤12.33	≤13.12
6	89.67-112.67	≤11.63	≤12.67
15	93.33-113.75	≤12.83	≤13.04

THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta9-tetrahydrocannabinol

Table 5. Comparison of the causes of death and age ranges between the RTI and non-RTI groups

Group	N	Mean ± SD, median (years old)	Range (yrs old)	*p*-value
RTI	43	27.14±10.06, 25.00	15-66	0.020
Non-RTI	37	34.81±14.75, 31.00	15-79	
Total	80	30.69±12.95, 27.00	15-79	

RTI, road traffic injury

RESULTS

Overall, 80 subjects were included in this study, comprising 43 RTI cases (53.75%) and 37 non-RTI cases (46.25%). There were only 3 females (3.75%) and 77 males (96.25%). The mean age of all the subjects at death was 30.69 ± 12.95 years (range = 15-79). All the RTI cases were motorcycle riders. The age of the subjects in the RTI group was significantly lower than that of the non-RTI group according to the Mann-Whitney U test (p = 0.020), as shown in Table 5. The non-RTI group consisted of cases of hanging, gunshot wounds, stab wounds, drowning, falls from height, electrocution, drug intoxication, carbon monoxide poisoning, and homicidal blunt head trauma. Information on the non-RTI group in this study is provided in Table 6. Comparison of the age of the subjects among three manners of death in the non-RTI group did not show any statistically significant difference according to the Kruskal-Wallis H test (p = 0.340).

Comparison of the cannabis profiles in blood and urine samples from the RTI and non-RTI groups found that the concentrations of THC and its two metabolites in blood in the RTI group were significantly higher than in the non-RTI group, whereas the concentrations of THC and its two metabolites in urine in these two groups did not show any statistically significant difference (Table 7). In addition, when classifying the cannabis profiles as recent and non-recent cannabis exposure based on the presence of THC and/or 11-OH-THC in blood and/or urine, it was found that 90.70% (39/43) of the subjects in the RTI group had recent cannabis exposure, compared to 72.97% (27/37) of the subjects in the non-RTI group. Contingency table chi-square analysis showed that the number of subjects who had recent cannabis exposure in the RTI group was significantly higher than in the non-RTI group (p = 0.044).

As the urinary cannabis profiles did not show any significant differences, the blood cannabis profiles were further analyzed for comparison among four groups: RTI, suicide, homicide, and other accidental deaths. The Kruskal-Wallis H test showed that there were significant differences in the blood THC, 11-OH-THC, and THC-COOH among these four groups (Table 8). Furthermore, when cut-off concentrations of blood THC at ≥2 ng/mL and ≥5 ng/mL were applied, it was found that 76.74% (33/43) and 58.14% (25/43) of the subjects in the RTI group had blood THC concentrations ≥2 ng/mL and ≥5 ng/mL, respectively.

Table 6. Information on the non-RTI group

Non-RTI group		N	Age	
Manner of death	**Cause of death**		**Mean ± SD, median (years old)**	**Range (years old)**
Suicide	Hanging, gunshot wound, fall from height, carbon monoxide poisoning	14	35.14±16.76, 30.50	17-79
Homicide	Gunshot wound, stab wound, blunt head trauma	9	29.00±11.59, 30.00	15-46
Other accident	Drowning, fall from height, electrocution, drug intoxication	14	38.21±14.26, 37.00	21-66
Total		37	34.41±14.95, 30.00	15-79

RTI, road traffic injury

Table 7. Comparison of the cannabis profiles in blood and urine between the RTI and non-RTI groups

Cannabis profiles	Mean ± SD, median (Range) (ng/mL)		*p*-value
	RTI	**Non-RTI**	
Blood			
THC	9.50±9.40, 7.39 (ND-40.92)	5.31±8.05, 1.38 (ND-35.91)	0.004*
11-OH-THC	1.98±2.16, 1.34 (ND-11.92)	0.84±1.37, 0.42 (ND-7.19)	0.001*
THC-COOH	39.34±35.26, 33.06 (0.63-168.91)	14.29±21.16, 7.04 (ND-109.67)	<0.001*
Urine			
THC	0.15±0.43, ND (ND-2.21)	0.13±0.40, ND (ND-1.76)	0.427
11-OH-THC	0.69±2.98, 0.25 (ND-19.67)	0.28±0.38, ND (ND-1.22)	0.988
THC-COOH	237.82±282.59, 91.25 (1.45-931.78)	139.89±200.52, 60.24 (3.76-860.19)	0.071

*ND, not detected; RTI, road traffic injury, THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta9-tetrahydrocannabinol

Table 8. Comparison of the blood cannabis profiles among four manners of death

Blood cannabis profiles	THC (ng/mL)	11-OH-THC (ng/mL)	THC-COOH (ng/mL)
RTI group			
Mean±SD	9.50±9.40	1.98±2.16	39.34±35.26
Median	7.39	1.34	33.06
RTI group			
Mean±SD	8.07±10.29	1.05±1.88	12.14±12.31
Median	4.95	0.53	8.60
Homicide			
Mean±SD	4.57±8.06	0.84±0.93	23.37±34.90
Median	1.16	0.46	14.15
Other accident			
Mean±SD	3.04±4.42	0.66±1.03	10.59±16.19
Median	0.99	0.30	3.29
p-value	0.015*	0.010*	<0.001*

RTI, road traffic injury

When considering the combination of use of alcohol and cannabis, the BAC ranges in the RTI and non-RTI groups were 0-229.85 mg/dL and 0-387.66 mg/dL, respectively, while the mean ± SD BAC in the RTI and non-RTI groups were 39.66 ± 38.36 mg/dL and 38.36 ± 93.02, respectively. The BAC in the RTI group was not significantly different from the BAC in the non-RTI group (p = 0.605). Interestingly, it was found that the majority of subjects in both groups had negative BAC results (72.09% (31/43) of RTI cases and 75.68% (28/37) of non-RTI cases). In addition, focusing on the RTI group, it was found that the median blood THC, 11-OH-THC, and THC-COOH concentrations in the subjects who had a BAC greater than 50 mg/dL were 8.72, 1.66, and 29.28 ng/mL, while the median blood THC, 11-OH-THC, and THC-COOH concentrations in the subjects who had a negative BAC were 5.24, 0.98, and 34.14 ng/mL, respectively. There was no significant difference in blood THC, 11-OH-THC, or THC-COOH concentrations between the subjects who had a BAC greater than 50 mg/dL and subjects who had a negative BAC (p = 0.731, 0.742, and 0.920, respectively).

Of the subjects using cannabis with other drugs, 28.75% (23/80) had used cannabis with other drugs. In the two groups, 18.60% (8/43) of the RTI subjects and 40.54% (15/37) of the non-RTI subjects had used other drugs with cannabis. Contingency table chi-square analysis showed that the number of subjects who had used other drugs with cannabis in the RTI group was significantly lower than that in the non-RTI group (p = 0.031). The mean ± SD and median blood THC concentrations of the subjects who had used cannabis without other drugs or medication were 11.04 ± 9.72 ng/mL and 8.72 ng/mL, while the mean ± SD and median blood THC concentrations of the subjects who had used cannabis with other drugs or medication were 2.77 ± 2.75 ng/mL and 2.68 ng/mL in the RTI group, showing that the blood THC concentrations of the subjects who had used cannabis without other drugs or medication were significantly higher than those of the subjects who had used cannabis with other drugs or medication (p = 0.010). The number of other drugs used with cannabis ranged from 1 to 8 drugs. The most common drugs found with cannabis in this study were mitragynine (13.75%), antihistamine (12.50%), ketamine (11.25%), benzodiazepine (10.00%), and methamphetamine (10.00%). Details of concomitant drugs found with cannabis in this study are shown in Table 9. Although statistical analysis could not be performed because some cells in Table 9 had less than 5 observations, it was found that mitragynine was predominant in the RTI group whereas heroin and benzodiazepine were predominant in the other accident groups (particularly drug intoxication).

Comparing the cannabis profiles in the blood and urine of the subjects who had used cannabis without drugs of abuse or medication with those of the subjects who had used cannabis with drugs of abuse or medication, it was again found that the concentrations of THC and its two metabolites in the subjects who had used cannabis without drugs of abuse or medication were significantly higher than those in the subjects who had used cannabis with drugs of abuse or medication (Table 10). However, comparison of the concentrations of THC and its two metabolites in urine between these two groups did not show any statistically difference (Table 10).

Table 9. Details of concomitant drugs found in subjects positive for cannabis

Drugs	RTI group	Suicide	Homicide	Other accident	Total percentage
Mitragynine	5	2	2	2	13.75% (11/80)
Antihistamine	4	1	2	3	12.50% (10/80)
Ketamine	4	1	1	3	11.25% (9/80)
Methamphetamine	4	1	1	2	10.00% (8/80)
Benzodiazepine	1	0	1	6	10.00% (8/80)
Heroin	2	0	1	4	8.75% (7/80)
Tramadol	1	1	2	3	8.75% (7/80)
Other drugs	1	1	1	4	8.75% (7/80)

RTI, road traffic injury

Table 10. Comparison of the cannabis profiles in blood and urine between the RTI and non-RTI groups

Cannabis profiles	Mean ± SD, median (range) (ng/mL)		*p*-value
	Cannabis without drugs	Cannabis with drugs	
Blood			
THC	9.40±9.79, 7.06 (ND-40.92)	3.03±4.04, 1.16 (ND-13.33)	0.001*
11-OH-THC	1.78±2.13, 0.94 (ND-11.92)	0.65±0.81, 0.30 (ND-2.82)	0.005*
THC-COOH	30.73±33.27, 18.81 (0.63-168.91)	20.38±27.86, 4.45 (ND-109.67)	0.045*
Urine			
THC	0.15±0.43, ND (ND-2.21)	0.12±0.38, ND (ND-1.63)	0.516
11-OH-THC	0.64±2.59, 0.25 (ND-19.67)	0.16±0.29, ND (ND-1.22)	0.075
THC-COOH	210.11±260.19, 93.95 (1.45-931.78)	148.93±227.62, 54.23 (3.76-860.19)	0.108

*ND, not detected; RTI, road traffic injury, THC, delta9-tetrahydrocannabinol; 11-OH-THC, 11-hydroxy-delta9-tetrahydrocannabinol; THC-COOH, 11-Nor-9-carboxy-delta 9-tetrahydrocannabinol

DISCUSSION

To the best of our knowledge, this is the first study that reports and compares the concentrations of THC and its two metabolites (11-OH-THC and THC-COOH) in blood and urine samples from Thai postmortem cases. As THC and its two metabolites are highly lipophilic molecules, postmortem blood concentrations of THC and its two metabolites are prone to postmortem distribution leading to limitation of interpretation of cannabis profiles in postmortem blood samples (6). For that reason, recent cannabis exposure in this study was interpreted mainly based on the presence of THC and/or 11-OH-THC in blood and/or urine. This study showed that the blood concentrations of THC in RTI cases were significantly higher than those in cases with other causes of death. A previous study reported mean and median blood THC concentrations in fatal RTI cases of 11.7 and 4.5 ng/mL, respectively (8). These figures are comparable to our study, with mean and median blood THC concentrations in the RTI cases of 9.50 and 7.39 ng/mL, respectively. In addition, the present study found that the majority of fatal RTI cases were recent cannabis users which is consistent with previous studies (8, 9). A previous study suggested that drivers who were recent cannabis users and who had a blood THC concentration of 8.2 ng/mL and 13.1 ng/mL showed driving impairment similar to BACs of 50 mg/dL and 80 mg/dL, respectively (11). In addition, a blood THC concentration of 5 ng/mL plus BAC of 50 mg/dL have been reported to produce driving impairment similar to a BAC of 80 mg/dL (11). Drummer, OH et al. reported adjusted odd ratios (OR) for injured drivers with THC levels of 1-4.9, ≥ 5, and ≥ 10 ng/mL of 1.6, 3.2, and 10, respectively, while the adjusted OR for injured drivers with a BAC of 50-100 mg/dL was 5.7 (12). Thus, a common cut-off for blood THC concentrations of 2 ng/mL and 5 ng/mL is applied in many countries in Europe and North America. Based on this finding, it could be implied that the majority of fatal RTI cases in this study were under the influence of cannabis because 76.74% and 58.14% of the subjects in the RTI group had a blood THC concentration of ≥ 2 ng/mL and ≥ 5 ng/mL, respectively. However, additional study should be performed to further elucidate the risk of driving while using cannabis in the Thai population. Currently, investigation of cases of driving under influence in Thailand is mandatory only for alcohol and methamphetamine. This result shows that investigation of driving under influence of cannabis in Thai people should be required because the majority of Thai RTI cases in this study had blood THC concentrations that were comparable to fatal RTI cases in previous studies (8, 9). The best indicator of driving under influence of cannabis was blood samples (7). Oral fluid can be useful because

it is easier to collect, but THC concentration in oral fluid is not closely associated with blood THC concentration, limiting the use of oral fluid for the investigation of driving under influence of cannabis (7). Additionally, blood THC concentrations rapidly decline after exposure, leading to difficulty with blood THC determination. Thus, timing of blood collection is crucial for interpretation and further research should be conducted to elucidate this finding. In addition, the effect of cannabis exposure on driving performance in living Thai people should be studied based on the results of previous reports (11, 12). Such research is fundamental for establishing the association between blood THC concentration and driving performance, and could lead to determination of a cut-off blood THC concentration for driving under influence of cannabis in Thai population.

This study shows that Thai people who used cannabis with other drugs or medication had blood THC, 11-OH-THC, and THC-COOH concentrations significantly less than Thai people who used cannabis without other drugs or medication. There is only limited data about the comparison of blood THC and its metabolite concentrations between cannabis abusers using other drugs or medication and cannabis abusers not using other drugs or medication because most data are focused on common conventional medications that are known to affect cannabinoid compounds (13). Ho, JJY et al.'s review reported that morphine did not have an effect on blood THC concentration (14). Thus, it could be possible that the presence of other drugs of abuse or medication might not directly affect blood THC and its metabolite concentration. However, the use of other drugs of abuse or medication might have an effect in that people may not need to use a high dose of cannabis because of the effect of other drugs of abuse or medication. Further study should be conducted to investigate the interaction between cannabis and other drugs of abuse or medication.

Previous studies have reported that marijuana users are prone to using other drugs, including hallucinogens, inhalants, prescription drugs (pain relievers and sedative-hypnotic drugs), and drugs of abuse (particularly cocaine and methamphetamine) (15, 16). However, the majority of subjects in this study had used cannabis without other drugs of abuse or medication. Kalayasiri, R. et al. reported that kratom (Mitragyna speciosa) leaves and kratom cocktails (which commonly contain antihistamine, tramadol, and benzodiazepine) are often consumed by cannabis users in Thailand (2). This study found that drugs commonly used with cannabis by Thai people include mitragynine (an alkaloid compound from kratom leaves) and antihistamine, consistent with findings from Kalayasiri, R. et al. (2). This result suggests that concomitant drug use with cannabis might depend on different peoples' behavior and geographical area.

Although there was significant difference in blood concentrations of THC and its two metabolites between RTI cases and non-RTI cases, there was no statistically significant difference in urinary concentrations of cannabis profiles between RTI and non-RTI cases. This result could be explained by the pharmacokinetics of cannabis. THC and its two metabolites are lipophilic molecules which can be distributed into adipose tissue and then released for excretion (6). Thus, urinary concentrations of THC and its two metabolites can result from both acute cannabis exposure and from accumulation from chronic cannabis exposure leading to longer than usual detection times of cannabis excretion in urine (6). This indicates that the urinary concentrations of THC and its two metabolites in this study did not come exclusively from acute cannabis exposure before death but also from past cannabis exposure. Desrosiers, NA, et al. reported that occasional cannabis smokers can test positive for THC and its two metabolites in blood for 6-30 hours, whereas frequent cannabis smokers can test positive for THC and its two metabolites in blood for more than 30 hours (17). Compared with urinary cannabis profiles, previous studies have shown that light cannabis smokers can test positive for urinary THC or its two metabolites for 24-120 hours, (18) whereas chronic cannabis users who come to a health facility for rehabilitation can present with positive detection for urinary THC-COOH for up to 30 days (19). When urinary cannabis profiles are affected by the accumulation from the past cannabis use, it can lead to a finding of no significant difference in urinary concentrations of cannabis profiles between RTI and non-RTI cases. Thus, using urinary cannabis profiles for medicolegal interpretation should be done cautiously,

particularly when THC-COOH is found only in urine because THC-COOH can be found for up to 30 days after cannabis exposure in cases of chronic cannabis abuse (19). This suggests that urinary cannabis profiles may not be suitable for proving acute physical impairment, including impaired driving capability. According to current Thai legislation, driving under the influence is compulsory only for the detection of blood alcohol concentration and methamphetamine in urine. Thus, if the government plans to enact new legislation related to driving under influence of cannabis, the use of blood samples should be considered for detection of THC and/or its two metabolites rather than using only urine for investigations.

The main limitation of this study is the disproportionately low number of females, with only three subjects included in this study. Thus, comparison of the blood and urinary cannabis profiles between female and male subjects could not be performed. In addition, the number of subjects who used cannabis with alcohol and drugs of abuse or medication were relatively small compared with the number of subjects who used cannabis without alcohol or drugs of abuse or medication which might have had an effect on the non-parametric statistical analysis. Further studies should be performed which include more female subjects.

CONCLUSIONS

Blood THC, 11-OH-THC, and THC-COOH concentrations in RTI cases are significantly higher than those in cases of other unnatural causes of death. The mean and median blood THC concentrations in the RTI cases were 9.50 and 7.39 ng/mL, respectively. The majority of fatal RTI cases in this study were recent cannabis users. In addition, blood THC, 11-OH-THC, and THC-COOH concentrations in subjects that used cannabis without drugs of abuse or medication were significantly higher than those in subjects who used cannabis with drugs of abuse or medication.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author's contribution

P.C.: conceptualization, literature review, methodology, data curation, data analysis, writing - original draft preparation; S.S.: method validation, data curation, data analysis; PP: conceptualization, literature review, methodology, review & editing, supervision. All authors have read and approved the final version of this manuscript that was submitted for publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Hasin D, Walsh C. Trends over time in adult cannabis use: A review of recent findings. Curr Opin Psychol. 2021;38:80-5.
2. Kalayasiri R, Boonthae S. Trends of cannabis use and related harms before and after legalization for recreational purpose in a developing country in Asia. BMC Public Health. 2023;23:911. PubMed PMID: 37208663
3. Angkurawaranon C, Jiraporncharoen W, Likhitsathian S, Thaikla K, Kanato M, Perngparn U, et al. Trends in the use of illicit substances in Thailand: Results from national household surveys. Drug Alcohol Rev. 2018;37:658-63.
4. Jayuphan J, Assanangkornchai S, Wichaidit W. Cannabis use behaviors and related harms among adults in Thailand by sex assigned at birth and age groups. J Health Sci Med Res. 2024;42:1-15.
5. Atisook R, Mochadaporn C, Chanthong P, Sriveerachai P, Zinboonyahgoon N. Prevalence and characteristics of medicinal cannabis use among chronic pain patients; A post- legalization study in a tertiary care setting in Thailand. Siriraj Med J. 2024;76:21-30.
6. Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers. 2007;4:1770-804.
7. Brubacher JR, Chan H, Erdelyi S, Macdonald S, Asbridge M, Mann RE, et al. Cannabis use as a risk factor for causing motor vehicle crashes: a prospective study. Addiction. 2019;114:1616-26.

8. Lemos NP, San Nicolas AC, Volk JA, Ingle EA, Williams CM. Driving Under the Influence of Marijuana Versus Driving and Dying Under the Influence of Marijuana: A Comparison of Blood Concentrations of Δ9-Tetrahydrocannabinol, 11-Hydroxy-Δ9-Tetrahydrocannabinol, 11-Nor-9-Carboxy-Δ9-Tetrahydrocannabinol and Other Cannabinoids in Arrested Drivers Versus Deceased Drivers. J Anal Toxicol. 2015;39:588-601.
9. Rooney B, Gouveia GJ, Isles N, Lawrence L, Brodie T, Grahovac Z, et al. Drugged Drivers Blood Concentrations in England and Wales Prior to the Introduction of Per Se Limits. J Anal Toxicol. 2017;41:140-5.
10. Scientific Working Group for Forensic Toxicology. Scientific Working Group for Forensic Toxicology (SWGTOX) standard practices for method validation in forensic toxicology. J Anal Toxicol. 2013;37:452-74.
11. Hartman RL, Brown TL, Milavetz G, Spurgin A, Pierce RS, Gorelick DA, et al. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend. 2015;154:25-37.
12. Drummer OH, Gerostamoulos D, Di Rago M, Woodford NW, Morris C, Frederiksen T, et al. Odds of culpability associated with use of impairing drugs in injured drivers in Victoria, Australia. Accid Anal Prev. 2020;135:105389. PubMed PMID: 31812899.
13. Qian Y, Gurley BJ, Markowitz JS. The Potential for Pharmacokinetic Interactions Between Cannabis Products and Conventional Medications. J Clin Psychopharmacol. 2019;39:462-71.
14. Ho JJY, Goh C, Leong CSA, Ng KY, Bakhtiar A. Evaluation of potential drug-drug interactions with medical cannabis. Clin Transl Sci. 2024;17(5):e13812. PubMed PMID: 38720531.
15. Wu LT, Pilowsky DJ, Schlenger WE. High prevalence of substance use disorders among adolescents who use marijuana and inhalants. Drug Alcohol Depend. 2005;78:23-32.
16. Zhang S, Wu S, Wu Q, Durkin DW, Marsiglia FF. Adolescent drug use initiation and transition into other drugs: A retrospective longitudinal examination across race/ethnicity. Addict Behav. 2021;113:106679. PubMed PMID: 33032193.
17. Desrosiers NA, Himes SK, Scheidweiler KB, Concheiro-Guisan M, Gorelick DA, Huestis MA. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. Clin Chem. 2014;60:631-43.
18. Brenneisen R, Meyer P, Chtioui H, Saugy M, Kamber M. Plasma and urine profiles of Delta9-tetrahydrocannabinol and its metabolites 11-hydroxy-Delta9-tetrahydrocannabinol and 11-nor-9-carboxy-Delta9-tetrahydrocannabinol after cannabis smoking by male volunteers to estimate recent consumption by athletes. Anal Bioanal Chem. 2010;396:2493-502.
19. Goodwin RS, Darwin WD, Chiang CN, Shih M, Li SH, Huestis MA. Urinary elimination of 11-nor-9-carboxy-delta9-tetrahydrocannnabinol in cannabis users during continuously monitored abstinence. J Anal Toxicol. 2008;32:562-9.

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Sex Estimation Using Radiographic Films of the Frontal Sinuses in Thai Populations

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ABSTRACT

OBJECTIVE This study aims to determine the forensic importance and applicability of the frontal sinus by evaluating its morphoscopic and morphometric characteristics in relation to sex.

METHODS Antero-posterior skull radiographs of 235 individuals (141 males and 94 females) were taken using a standardized procedure. Frontal sinus morphology was observed and classified. Specific measurements (A to D) were conducted to estimate sex by developing logistic regression equations.

RESULTS Frontal sinus symmetry was detected in 58.7% of the individuals. Morphometric analyses of frontal sinuses were only moderately correlated with the sex, with an area under the ROC curve of 0.629 (measurement A). The recommended cut-off score of measurement A was 6.47 cm, in which the sensitivity and specificity were 78.7% and 59.6%, respectively.

CONCLUSIONS This study found significant individual variation in the frontal sinus patterns. Evaluating the frontal sinus could be used as an adjunct to other methods of personal identification, particularly for sex estimation.

KEYWORDS frontal sinus, sex, forensic radiology, skull radiograph

INTRODUCTION

Human identification is a complex, systematic, and standardized process involving comparison of individual information about a missing person, including biological and personal information, with comparable data gathered from unknown human remains. Scientific techniques such as fingerprint analysis, DNA and dental matching, and anthropological methods are mentioned as common practices for personal identification (1, 2). To identify unknown deceased individuals, human identification is crucial in scenarios like mass disasters, accidents, and criminal investigations. Nevertheless, there are limitations of traditional identification methods like fingerprinting and DNA analysis, particularly when remains are decomposed, burnt, or when DNA is compromised. Anthropological techniques can be applied in these situations. Cranial radiography is one of the potentially useful identification techniques when only a portion of the skull may be available.

Examination using cranial radiography is recognized as a standard procedure in dental and medical clinics. To date, there have been many articles in which personal identification was achieved by comparing antemortem and postmortem radiographs of a particular part of a cranium (3-6). Using the frontal sinus became popular for human identification because of its unique characteristics. This structure consists of bilateral, irregularly shaped,

air-containing cavities in the frontal bone that can vary between individuals and can be visible with radiographic techniques (7). These factors make the frontal sinus suitable for analysis in an adult population (6, 7).

Sexual dimorphism is recognizable in several anatomical characteristics of the skull, such as the foramen magnum (8) and the mandible (9). Numerous studies have proposed that the frontal sinus could be helpful in accurately determining sex. Yoshino et al. suggested that the frontal sinuses of males are larger than those of females (6) which is in agreement with a study by Buckland-Wright (10). In females, the frontal sinuses are smaller, and their superior margins are more scalloped (11). A 2023 study of the frontal sinus in the Thai population by Pangsorn and Soodchuen (12) analyzed 270 cranial computed tomography (CT) images to evaluate sex determination based on the frontal sinus parameters. They proposed using parameters of frontal sinuses based on the following seven discrete variables: the absence or presence of frontal sinuses, scalloping, complete and incomplete septal lengths, max height and width, max total width, and max antero-posterior (AP) diameter. Their results showed that measurements of frontal sinuses (max height and width, max AP diameter, and total max width) have the potential to be used in correctly identifying sex. However, the question arises whether the results of CT examination can be compared with those based on radiographic examination. Plain x-ray investigation is still very important in routine forensic practice in Thailand because the method is readily accessible and cost-effective. To the best of our knowledge, no research has been done on determining sex from frontal sinus patterns in a Thai population using radiographic analysis. Because of variations in genetics and environment, the results from a non-Thai population may differ from those from the Thai population.

The purpose of this study was to evaluate the reliability of radiographic examination of the frontal sinus for sex estimation in a Thai population. The study analyzed the frontal sinus category and size using standardized measurements of plain X-rays of the frontal sinuses.

METHODS

Sample

This study was approved on October 20, 2023 by the Research Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Protocol No. 716/2566 (IRB2).

The sample size was calculated using nQuery Sample Size Software (nQuery Advanced 8.7) (Statsols, Boston, MA). Between January 2019 and July 2024, adult cadavers which underwent autopsy in the Forensic Pathology Unit, Department of Forensic Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University were used as the subjects in this study. All cadavers were Thai nationals with an age range of 20-45 years.

It is generally accepted that the frontal sinus first appears in children as early as age 5 or 6. This structure becomes completely developed around the age of 20, and generally remains stable until advancing age when atrophic changes begin to appear (13-18). Deceased individuals with sinus pathologies such as mucosal thickenings or any masses in the sinuses were excluded from this study. In addition, individuals with a history of cranial trauma or surgery, a clinical history of endocrine disturbances, nutritional disorders, or hereditary facial asymmetries were excluded from the study. Subjects without an appearance of frontal sinuses were also excluded from this study.

Antero-posterior radiographs of skulls were taken with a mobile X-ray apparatus (SOURCE-RAY SR130, Source-Ray, Inc., NY) at 80 kvp, 3.0 mA, and a 0.1-minute exposure time. To ensure a symmetrical and clear image of the skull, the bodies were positioned with the chin slightly lifted, the back of the head against the image detector, and the central ray focused at the nasion. The examination of the radiographic images was carried out using RadiAnt DICOM Viewer software (version 2020.2.3 (32-bit)) (Fujidenolo Solutions Co., Ltd., Komaki City, Aichi, Japan) and a monitor.

Frontal sinus category and measurement protocol

The frontal sinus shape was classified according to the bilateral symmetry or asymmetry, the high point of each side, and the outline of upper borders (Figure 1 and Table 1). The shape of the frontal sinus was evaluated using the standardized measurement protocol adapted from De Andrade

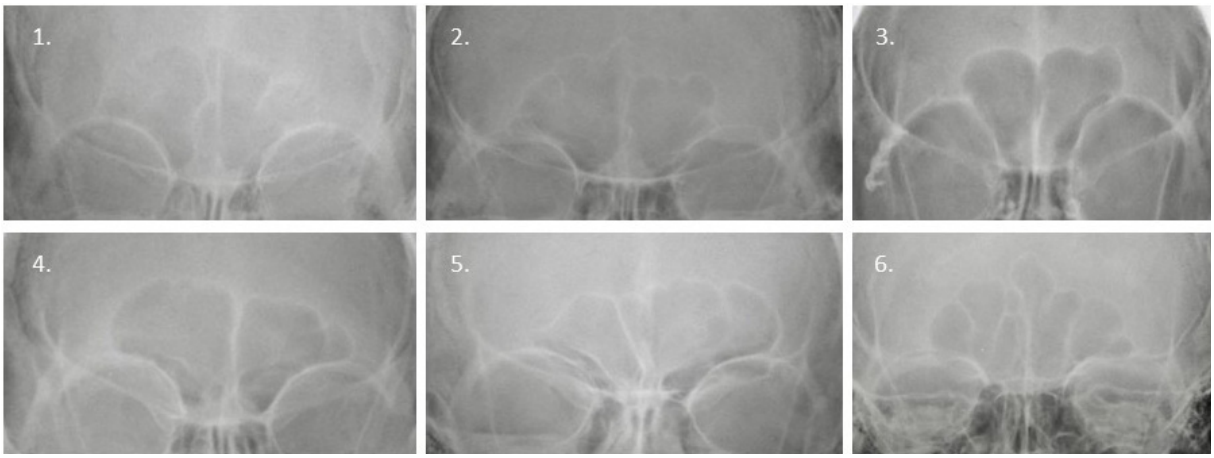

Figure 1. Frontal sinus (categories 1 to 6)

Table 1. Definition of frontal sinus categories

Category	Definition
1	Frontal sinuses with symmetrical shape of partition and chamber
2	Frontal sinuses with two equally high points
3	Frontal sinuses with open-curve lobulations (the highest curve is identified, but the highest point is difficult to determine)
4	Frontal sinuses with plateau lobulations (the highest point is not evident)
5	The air-containing cavity of the frontal bone as a part of the frontal sinus
6	Frontal sinuses in triangular shape without two distinct highest points because both sinuses coincide at the vertex of the triangle

Quintanilha Ribeiro (19). First, a baseline was drawn horizontally along the upper limit of both orbits. Then four more lines were drawn perpendicular to the baseline (Figure 2). The first (A) and second (B) lines delineate the maximum lateral limit of the right and left frontal sinuses. Another two lines (C and D) pass through the highest point of the right and left frontal sinuses. From these lines, the four measurements can be conducted (Table 2).

Anatomical variations can be encountered. Adapting the previously described techniques is necessary when measuring anatomy that does not fit a traditional architectural pattern (19).

1. When a frontal sinus has two equally high points, measure the one that is closest to the intersinus septum.
2. When the highest point is difficult to locate because the sinus has open-curve or plateau lobulation, measure the point at the middle of the lobulation.
3. Any air-filled frontal sinus cavity is considered as a part of the frontal sinus and needs to be measured.

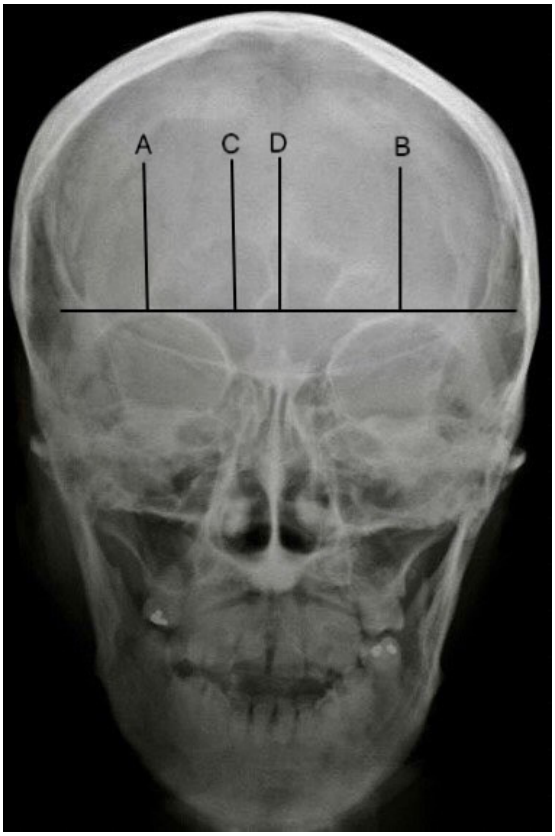

Figure 2. Landmarks for measurement protocol

Table 2. Measurement definitions (adapted from Ribeiro (19))

Measurement	Definition
A	The maximum diameter of the frontal sinuses (lines A and B)
B	The distance between the highest points of the left and right frontal sinuses (lines C and D)
C	The distance between the maximum lateral limit and the highest point of the left frontal sinus (lines A and C)
D	The distance between the maximum lateral limit and the highest point of the right frontal sinus (lines B and D)

4. In cases where the frontal sinuses do not have two separate highest points because of their triangular shape, the highest point of the vertex is used for measurement, and the list measurement of B is zero.

Statistical analysis

The statistical analysis was performed using the SPSS software package (version 26 for Windows; SPSS Inc., Chicago, IL). Statistical significance was considered as a *p*-value of less than 0.05. Quantitative data such as mean values, range, and standard deviations were calculated. Categorical data are displayed as numbers and a percentages. The t-test and chi-square test were performed to determine whether there was a significant difference between males and females. A logistic regression equation was used to analyze the association of measurement values and sex as ROC curves and the area under the curve. A cut-off score of the most significant statistical data was selected based on the sensitivity and specificity of the ROC curve. To test reliability, 30 skull radiographic images were randomly selected and reassessed for both intra- and inter-observer errors.

RESULTS

A total of 235 cadavers were included, consisting of 141 males and 94 females. The mean age of males and females in this study population was 35.25 (standard deviation [SD] = 7.01) years and 33.34 (SD = 7.35) years, respectively. The manner of death of the 235 subjects was as follows: 131 subjects (55.7%) were due to natural diseases, 55 subjects (23.4%) were due to car accidents, 39 subjects (16.6%) were due to suicide, and 10 subjects (4.3%) were homicides.

Table 3 illustrates the frequency of each type of frontal sinus category among the study group. The most common frontal sinus category observed in this study was category 1 (58.7%), followed by category 3 (18.7%), category 2 (6.8%), category 4 (6.4%), category 6 (6.0%), and category 5 (3.4%). However, there was a statistically insignificant sex difference in the frequencies of the frontal sinus category ($p = 0.226$).

Table 3. Frequency of frontal sinus category

Frontal sinus category	Male n=141 (%)	Female n=94 (%)	Total n=235 (%)
1	79 (56.0)	59 (62.8)	138 (58.7)
2	6 (4.3)	10 (10.6)	16 (6.8)
3	30 (21.3)	14 (14.9)	44 (18.7)
4	11 (7.8)	4 (4.3)	15 (6.4)
5	5 (3.5)	3 (4.3)	8 (3.4)
6	10 (7.1)	4 (4.3)	14 (6.0)

Table 4. Statistical data of frontal sinus measurements

Measurement	Sex	Mean (cm)	Standard deviation (cm)	*p*-value
A	Male	7.04	1.92	0.001*
	Female	6.21	1.65	
B	Male	2.04	1.17	0.990
	Female	2.01	1.11	
C	Male	2.37	1.20	0.019
	Female	2.00	1.09	
D	Male	2.68	1.13	0.002*
	Female	2.24	0.96	

* $p < 0.01$

The frequency of all frontal sinus measurements is shown in Table 4. The frontal sinuses were found to be larger in males than females, with the difference between males and females statistically significant for measurements A and D ($p < 0.01$). Univariable logistic analysis showed that the areas under the ROC curve in measurement A was 0.629 and 0.613 in measurement D, suggesting a moderate predictive performance. The recommended cut-off score of measurement A, which allows for the best sensitivity and specificity, is 6.47 (sensitivity 78.7%, specificity 59.6%).

The reliability of both morphoscopic and morphometric characteristics was also investigated. Using Cohen's Kappa coefficient, the average intra-class correlation coefficient (ICC) was 0.95 for intra-observer reliability and 0.91 for inter-observer reliability. Based on a 95% confidence interval, ICC values higher than 0.9 indicate excellent reliability (20).

DISCUSSION

Zukerkandl and colleague in 1895 were the first to notice the uniqueness of the frontal sinus, highlighting its asymmetrical morphology (21). Culbert and Law introduced the first case of human identification using morphological analysis of the frontal sinus to be accepted in a US court (22). Since then, there has been significant progress in the study of several frontal sinus features (1, 3, 12). Previous studies have concentrated on taking several frontal sinus measurements and integrating the probability of each measurement for analysis (19, 23). The strength of the metric analysis of the frontal sinus is supported by probability analysis of probability assessment (24). In accordance with previous studies, the present study used plain skull x-rays, and analyzed results using logistic regression.

Previous studies have looked at the frontal sinus using computed tomographic techniques (25-27). However, plain x-ray investigations continue to play an important role in routine forensic work for human identification in Thailand because of their reliability, low-cost, and easy accessibility, which has led to the development of technical and comprehensive parameters, e.g., the evaluation of the morphological shape of the frontal sinus (28, 29). Christensen (2005) employed elliptical Fourier analysis to compare Euclidian distances, but that method is very resource-intensive and complex (30). The present study attempted to develop a low-cost solution for the Thailand context, making it more appropriate for the financial constraints that are faced by disaster management organizations in Thailand. In addition, this study marks an initial attempt at personal identification based on standardized measurements of radiographic images of the frontal sinuses as mentioned by De Andrade Quintanilha Ribeiro and provides a simple and cost-effective system for identifying the sex of unknown remains (19).

The present study utilized plain skull x-rays in an AP radiograph projection, as this allows the frontal sinus to be assessed with minimal distortion. A difference in the position of the skull during radiographic examination can potentially generate differences in measurements, leading to possible misrepresentation of the true anatomical dimensions. The radiological images produced by AP and PA views are dissimilar in both size and clarity, even though the angles are similar. These two views provide different size measurements of the frontal sinus because the frontal sinuses are not located at the same distance from the film. In the AP view used in this study, the frontal sinus is farther away from the film, while the frontal sinus is closer to the film in the PA view, leading to a difference in magnification (31). In this study, it was often not possible to use the radiograph approach in PA projection due to the limitations resulting from position of the deceased lying in the supine position.

This study attempted to categorize different types of frontal sinus shapes to investigate how they could be used to determine sex and contribute to the field of forensic medicine. The radiological images of the frontal sinus revealed various forms in this study, differing in width, and height, as well as number and shape of partitions and chambers (31, 32). In this study, symmetry of the frontal sinus (category 1) was identified in 58.7% of the individuals, whereas Taniguchi et al. obtained 43.1% symmetry in a Japanese population (33). The results of the present study are consistent with those of David and Saxena (34), who observed a symmetry of frontal sinus in 58.0% of the study group. There can be several anatomical variations in size and shape. Unusual conditions can include asymmetrical sinuses or different shapes of lobulation. Generally speaking, an asymmetrical shape of the frontal sinuses on the two sides results from unequal reabsorption of the diploë during the development of the frontal sinus (35). Some studies have reported that the observed differences in frontal sinus morphology are not statistically significant. These differences can be ascribed to racial and geographic characteristics as well as to the different techniques used in each study (36).

Previous research has verified that males often have a larger frontal sinus than females (6, 7, 29, 31, 37). The results in this study are in accordance

with those of previous studies, including that the mean values of the frontal sinus measurements A and D in males are significantly larger than those of females, e.g., the same result was observed by Camargo et al. (28). This finding can be explained by the fact that males typically have larger skulls than females (38-40). The measurements B and C of males in the present study were larger than those of females, but the difference was not statistically significant. Inherent variability of the morphology of the frontal sinus was also observed in this study. We considered using a cut-off score with the best value to maximize both sensitivity and specificity. As a result, we recommend a cut-off score of 6.47, which provides moderate predictive accuracy in discriminating between males and females. There are possible reasons that the results of this study showed a lower accuracy than those of previous studies (25, 26, 28). The main reason is that the configuration of the frontal sinus in different populations is influenced by both genetics and environmental variables, e.g., nutrition, hormones, and muscular attachment (29, 31).

While CT scans generally provide higher resolution images, radiographic analysis of frontal sinus morphology is straightforward, lower cost, not time-consuming, and easy for a forensic practitioner to utilize. It can be done with a single radiograph, which is typically taken during postmortem investigation. However, some limitations of this study should be considered. Our study sample may not be representative of the general Thai population because this study included only forensic autopsy cases. A larger sample might provide better results. Newer frontal sinus parameters should also be established to determine sex more accurately.

CONCLUSIONS

In forensic practice, sex determination in unidentified individuals is one of the most frequent and challenging areas. Several methods have been established in an effort to increase the accuracy of the determination of sex. This study attempted to evaluate frontal sinuses as a means of determining sex based on sinus patterns and measurements. The method described here should encourage wider use of radiographic analysis of the frontal sinuses in sex determination.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contribution

B.N.: conceptualization, methodology, data collection, data analysis, writing - draft; V.V.: supervision, conceptualization, methodology, data analysis, writing – review and editing.

REFERENCES

1. Cameriere R, Scendoni R, Lin Z, Milani C, Palacio L, Turiello M, Ferrante L. Analysis of frontal sinuses for personal identification in a Chinese sample using a new code number. J Forensic Sci. 2020;65:46–51.
2. Chantharawetchakun T, Vachirawongsakorn V. Age estimation in the Thai male population using epiphyseal union of the medial clavicle. Chiang Mai Med J. 2021;60:149-55.
3. Alves CP, Costa C, Michel-Crosato E, Biazevic M. Use of the frontal sinus to evaluate sexual dimorphism in a Brazilian sample. Forensic Imaging. 2023;33:200548.
4. Christoloukas N, Mitsea A, Rontogianni A, Angelopoulos C. Gender determination based on CBCT maxillary sinus analysis: a systematic review. Diagnostics. 2023;13:3536. PubMed PMID: 38066777
5. Wen H, Wu W, Fan F, Liao P, Chen H, Zhang Y, et al. Human identification performed with skull's sphenoid sinus based on deep learning. Int J Legal Med. 2022;136:1067–74.
6. Yoshino M, Miyasaka S, Sato H, Seta S. Classification system of frontal sinus patterns by radiography: Its application to identification of unknown skeletal remains. Forensic Sci Int. 1987;34:289–99.
7. Schuller A. A note on the identification of skulls by X-ray pictures of the frontal sinuses. Med J Aust. 1943; 1:554-6.
8. Tambawala S, Karjodkar F, Sansare K, Prakash N, Dora A. Sexual dimorphism of foramen magnum using Cone Beam Computed Tomography. J Forensic Leg Med. 2016;44:29–34.
9. Esfehani M, Ghasemi M, Katiraee A, Tofangchiha M, Alizadeh A, TaghaviDamghani F, et al. Forensic Gender

Determination by Using Mandibular Morphometric Indices an Iranian Population: A Panoramic Radiographic Cross-Sectional Study. J Imaging 2023;9:40. PubMed PMID: 36826959
10. Buckland-Wright J. A radiographic examination of frontal sinuses in early British populations. Man. 1970; 5: 512-7.
11. Krogman W, Iscan M. The human skeleton in forensic medicine, 2nd ed. Springfield, IL: Charles C. Thomas; 1986. p. 125-6.
12. Pangsorn A, Soodchuen S. A computed tomography assessment of frontal sinus for sex determination in the Thai population. J Med Health Sci. 2023;30:104-13.
13. Bilgin S, Kantarcı U, Duymus M, Yildirim C, Ercakmak B, Orman G, et al. Association between frontal sinus development and persistent metopic suture. Folia Morphol. 2013;72:306-10.
14. Haglund W. Remains identification by frontal sinus radiographs. J Forensic Sci. 1992;37:1207. PubMed PMID: 1285776
15. Harris A, Wood R, Nortje C, Thomas C. Gender and ethnic differences of the radiographic image of the frontal region. J Forensic Odontostomatol. 1987;5:51–7.
16. Marques J, Musse J, Gois B, Galvão L, Paranhos L. Cone-Beam computed tomography analysis of the frontal sinus in forensic investigation. Int J Morphol. 2014;32:660-5.
17. Nambiar P, Naidu M, Subramaniam K. Anatomical variability of the frontal sinuses and their application in forensic identification. Clin Anat. 1999;12:16–9.
18. Patil N, Karjodkar F, Sontakke S, Sansare K, Salvi R. Uniqueness of radiographic patterns of the frontal sinus for personal identification. Imaging Sci Dent. 2012;42:213–7.
19. Ribeiro F. Standardized measurements of radiographic films of the frontal sinuses: an aid to identifying unknown persons. Ear Nose Throat J. 2000;79:26-8, 30, 32-3.
20. Koo T, Li M. A guideline of selecting and reporting intra-class correlation coefficients for reliability research. J Chiropr Med. 2016;15:155-63.
21. Zukerkandl E, Lichtwitz L, Garnault P. vol 1., Anatomy of the frontal sinus. In: Normal and pathological anatomy of the nasal cavity. Paris: G Masson; 1895. p. 349-61.
22. Culbert Wl, Law FM. Identification by comparison of roentgenograms of nasal accessory sinuses and mastoid processes. JAMA. 1927;88:1634-6.
23. Kullman L, Eklund B, Grundin R. The value of the frontal sinus in identification of unknown persons. J Forensic Odontostomatol. 1990;8:3-10.
24. Chiba M, Terazawa K. Estimation of stature from somatometry of skull. Forensic Sci Int. 1998;97:87-92.
25. Akhlaghi M, Bakhtavar K, Moarefdoost J, Kamali A, Rafeifar S. Frontal sinus parameters in computed tomography and sex determination. Legal Medicine (Tokyo). 2016;19:22-7.
26. Rao K, Doppalapudi R, Al-Shammari N, Patil S, Vundavalli S, Alam M. Evaluation of frontal sinus index in establishing sex dimorphism using three-dimensional cone beam computed tomography in Northern Saudi Arabian population. J Forensic Sci Med. 2022;8:1-5.
27. Silva R, Picoli F, Botelho T, Resende R, Franco A. Forensic identification of decomposed human body through comparison between ante-mortem and post-mortem CT Images of Frontal Sinuses: Case report. Acta Stomatol Croat. 2017;51:227-31.
28. Camargo J, Daruge E, Prado F, Caria P, Alves M, Silva R, et al. The frontal sinus morphology in radiographs of Brazilian subjects: Its forensic importance. Braz J Morphol Sci. 2007;24:239-43.
29. Verma S, Mahima V, Patil K. Radiomorphometric analysis of frontal sinus for sex determination. J Forensic Dent Sci. 2014;6:177-82.
30. Christensen AM. Testing the reliability of frontal sinuses in positive identification. J Forensic Sci. 2005; 50:18-22.
31. Quatrehomme G, Fronty P, Sapanet M, Grévin G, Bailet P, Ollier A. Identification of frontal sinus pattern in forensic anthropology. Forensic Sci Int. 1996; 83:147-53.
32. Ubelaker D. Positive identification from the radiographic comparison of frontal sinus patterns. In: Rathbun T, Buikstra J, editors. Human Identification. Springfield, IL: Charles C. Thomas; 1984. p. 399-411.
33. Taniguchi M, Sakoda S, Kano T, Zhu B, Kamikodai Y, Fujita M, et al. Possible use of nasal septum and frontal sinus patterns to radiographic identification of unknown human remains. Osaka City Med J. 2003; 49:31-8.
34. David M, Saxena R. Use of frontal sinus and nasal septum patterns as an aid in personal identification: A digital radiographic pilot study. J Forensic Dent Sci. 2010;2:77-80.
35. Soman B, Sujatha G, Lingappa A. Morphometric evaluation of the frontal sinus in relation to age and gender in subjects residing in Davangere, Karnataka. J Forensic Dent Sci. 2016;8:57. PubMed PMID: 27051227
36. Danesh Sani S, Bavandi R, Esmaili M. Frontal sinus agenesis using computed tomography. J Craniof Surg. 2011;22:e48-51. PubMed PMID: 22134322
37. Pondé J, Andrade R, Via J, Metzger P, Teles A. Anatomical Variations of the frontal sinus. Int J Morphol. 2008;26:803-8.
38. Rooppakhun S, Surasith P, Vatanapatimakul N, Kaewprom Y, Sitthiseripratip K. Craniometric study of Thai skull based on three-dimensional computed tomography (CT) data. J Med Assoc Thai. 2010;93:90-8.
39. Ruenhunsa S, Vachirawongsakorn V. Cranial thickness in relation to age, gender and head circumference in Thai population. Chula Med J. 2022;66:337-42.
40. Sangvichien S, Boonkaew K, Chuncharunee A, Komoltri C, Piyawinitwong S, Wongsawat A, et al. Sex determination in Thai skulls by using craniometry: multiple logistic regression analysis. Siriraj Med J. 2007;59: 216-21.

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Development of an Auditing Tool for Clinical Occupational Health Services: A Modified Delphi Technique

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ABSTRACT

OBJECTIVE This study aim to develop a comprehensive auditing tool for clinical occupational health services (OHS) in corporate settings.

METHODS The design used a modified Delphi technique. The study was comprised of four steps: questionnaire construction and panelist selection, two rounds of questionnaires, and consensus determination. The participating experts included 31 occupational health professionals from 7 countries, representing management, occupational medicine, and auditing roles. Two rounds of questionnaires were administered to achieve 80.0% agreement on essential activities across the 7 key domains.

RESULTS The Delphi process yielded an audit tool encompassing 62 activities across seven domains: policy management (4 activities, 100.0% consensus), fitness for work assessment (7 activities, 85.7% consensus), medical surveillance programs (13 activities, 100% consensus), return to work assessment (7 activities, 71.4% consensus), occupational disease management (10 activities, 80.0% consensus), medical emergency preparedness (15 activities, 86.9% consensus), and health promotion (6 activities, 66.7% consensus). Experts' backgrounds influenced their focus, with hospital-based physicians emphasizing clinical protocols, company-based practitioners stressing implementation, management prioritizing governance, and auditors ensuring comprehensive assessments.

CONCLUSIONS This auditing tool required consideration of 7 domains, where experts rated the policy management and medical surveillance processes as the most important, whereas the domain of health promotion had the lowest importance score. This tool can help guide organizations in strengthening the foundational domains of OHS.

KEYWORDS basic occupational health services; audit tool; modified Delphi technique

INTRODUCTION

According to an International Labour Organization (ILO) report in 2023, the global landscape of occupational hazards showed concerning trends, with over 395 million non-fatal work injuries and 2.93 million work-related deaths recorded in 2019, marking a 12.0% increase since 2000. This increase can be attributed to multiple factors, including increased workplace risk exposure, a 26.0% growth in the global workforce, and improved diagnostic capabilities. Enhancing workplace occupational safety and health management systems (OSHMS) is needed (1). OSHMS represents a complementary approach to workplace

health and safety. It provides a systematic administrative framework guided by international standards, such as BS 8800 (2), OHSAS 18001 (3), and ISO 45001 (4). However, OSHMS should not be directly equated with a safe work system, as management systems focus on administrative aspects rather than practical implementation. The limited focus of OSHMS on clinical activities and medical perspectives highlights the essential role of occupational health services (OHS) in providing direct medical care and health surveillance (5). OHS operates within a comprehensive framework encompassing disease detection, injury prevention, and promoting worker well-being (6). The effectiveness of OHS depends on ensuring comprehensive coverage, implementing evidence-based practices, utilizing multi-professional approaches, and maintaining strong integration with workplace systems (7).

Regulatory frameworks for OHS vary significantly across countries. In terms of legislation, the United States follows the OSHA standards (8), while the United Kingdom implements the Health and Safety at Work Act (9). Within the Association of Southeast Asian Nations (ASEAN), Singapore and Malaysia, both influenced by British law, have developed comprehensive systems through the Workplace Safety and Health Act of 2006 (10) and the Occupational Safety and Health Act of 1994 (11), respectively. These frameworks emphasize risk management, self-regulation, and worker consultation. In contrast, Thailand's legal framework, the Ministerial Regulation on Employees' Health Examination (12), places less emphasis on welfare provisions and workplace dialogue (13). Beyond legislation, guidance-based frameworks have been used, such as the UK's SEQOHS (14) and the American College of Occupational and Environmental Medicine's (ACOEM) Excellence in Corporate Health Achievement Award (15). These approaches offer flexibility, encourage stakeholder engagement, and allow for quicker adaptation to emerging risks. Corporate social responsibility codes have also become increasingly important (15).

A previous study in 2022 reported that most enterprises provided only legally mandated services, with expanded service delivery influenced by corporate policies and the presence of on-site occupational physicians (16). Similarly, a 2019 study on occupational health audit practices revealed inconsistencies in audit implementation and limited dissemination of findings (17), whereas a 2015 study demonstrated that peer-review audit processes significantly improved report quality and reduced client complaints (18). These findings underscore the need for a standardized, comprehensive framework to evaluate clinical OHS performance across diverse organizational and national contexts.

Evaluation instruments can be developed using several research methods, such as systematic reviews or qualitative research (19). However, the audit framework must remain responsive to emerging workplace hazards and evolving healthcare delivery systems (20, 21). Given the complex nature of OHS quality standards and the need for comprehensive expert input, structured consensus-building methods are essential. For this study, a modified Delphi technique was chosen over the traditional one because predefined items had already been developed through an extensive literature review. This approach allows for efficient, structured evaluation, making it more practical given the time constraints and geographic dispersion of study participants (22).

Despite the extensive literature on OHS and various quality frameworks, there remains a significant gap in comprehensive tools for auditing clinical OHS across different settings and contexts. For that reason, this study aimed to develop a consensus-based audit tool to enhance practical aspects of clinical OHS delivery using the modified Delphi technique.

METHODS

Study design

A modified Delphi technique research design was employed between January 2024 and May 2024.

Study processes

The following four methodology steps were used: 1) questionnaire construction and expert recruitment, 2) first-round agreement of experts in the clinical activities of OHS, 3) second-round agreement of experts in the clinical activities of OHS, and, 4) consensus of the audit tool for clinical occupational health services (Figure 1).

Step 1. Questionnaire construction and expert recruitment. Experts in occupational health science were identified through conference participation,

referrals, and professional networks and were invited to participate in the study. The panel comprised 31 experts from diverse backgrounds in occupational health science.

Step 2. First-round questionnaire. The initial questionnaire was distributed to the expert panel by email with a link to an online survey platform. Experts were asked to rate the relevance of each item on a 5-point Likert scale and to provide additional comments or suggestions. Responses were collected over two months. The research team then analyzed the responses and calculated statistical measures using a more than 80.0% confidence level of agreement technique which meant that the sum of the proportions of levels 4 (agree) and 5 (totally agree) reached at least 80.0% (23).

Step 3. Second round questionnaire. This modified questionnaire was sent to the same expert panel. The experts were asked to review the group's responses and initial ratings, reconsider their responses, and potentially revise their judgments. This round allowed experts to clarify their views and help the study move towards a consensus. The responses were collected and analyzed.

Step 4. Consensus determination. After the second round, final analyses were conducted to determine which items had reached consensus based on an 80% confidence level of agreement technique. The final output was a consensus- based audit tool for the clinical aspects of occupational health services.

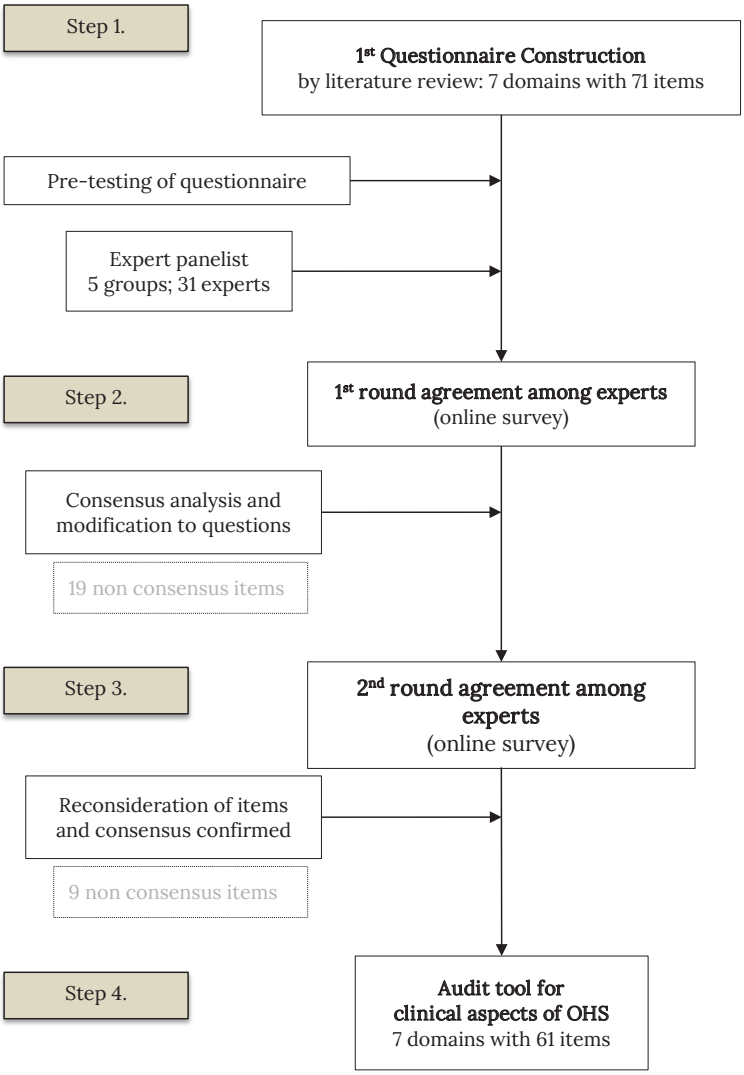

Figure 1. The modified Delphi method used in this study

Expert panel selection

The panel of 31 experts were purposively sampled. The number of experts was calculated according to the minimum required number of participants for the modified Delphi technique in order to detect the slightest discrepancy of opinion among 17 people (24). Experts were recruited from the USA, Bulgaria, Malaysia, Singapore, the Philippines, Indonesia, and Thailand. The expert panelists consisted of experts with the qualification of having experience in their position and specialization for at least 5 years and were classified into 5 groups: 1) individuals who had practiced in roles and positions of management, 2) occupational health physicians (OHP) working at a hospital/occupational medicine clinic, 3) OHPs working at a company, 4) individuals with an academic background relating to occupational health studies, and 5) individuals working as an auditor in quality assessment or on evaluations of occupational health and safety.

Research tools

There were two questionnaires: the first-round questionnaire was comprised of questions regarding the experts' background and ratings of domains and activities of clinical OHS; the second-round questionnaire was comprised of ratings and consensus measurements of domains and activities of clinical OHS.

The first-round questionnaire was developed based on a comprehensive literature review to identify key concepts and current knowledge in the field of OHS. Based on this review, the questionnaire was developed, focusing on 7 domains: policy management, fitness for work evaluation, medical surveillance program, return to work evaluation, occupational disease management, first-aid and medical emergency preparedness, and health promotion. The questionnaire was divided into 7 domains with a total of 71 activities. The questionnaire validity test was performed by 3 validators who were occupational physicians but not researchers. Item objective congruence (IOC) was used to assess the questionnaire content validity. An IOC index between 0.5 and 1.00 suggests that the question is acceptable (25).

The second-round questionnaire was developed by incorporating the statistical summary of the first-round responses and modifications to the items suggested by the experts.

Data collection

An online survey platform was sent to each panel member through an invitation email with a link to both questionnaires. The email requested the participant's consent to participate, and the responses were recorded anonymously. Each of the two rounds lasted two months, with three reminder emails sent to the panelists to remind them to complete the questionnaire.

Data analysis

The demographics of the experts were analyzed, and their expertise and years of workplace experience were evaluated. The consensus agreement was analyzed using a 5-point Likert scale for each item. The questions were analyzed using an agreement technique with a confidence level of > 80.0% for both questionnaire rounds. Data was analyzed using IBM SPSS Statistics, version 28.0 (IBM Corp., Armonk, NY, USA). Consensus on the audit tool was achieved after two rounds of the agreement technique. All domain questions were used to construct the audit tool for clinical OHS.

Ethical considerations

Ethical approval for this study (HE661325) was obtained from the Ethics Committee of Khon Kaen University. This study was exempt from review by the institutional review board, and the data were collected anonymously and were uninfluenced by the research team.

RESULTS

The results comprised the demographic data of the experts, the first and second rounds of agreement of experts on the clinical activities in OHS, and consensus on the audit tool for clinical occupational health services.

The demographic data of experts

A total of 31 experts from seven countries (Thailand (13), Singapore (6), Malaysia (5), the USA (4), Bulgaria (1), Indonesia (1), and the Philippines (1)) were included in the study to ensure diverse perspectives. The experts' demographic data were categorized according to their roles and sectors. Managerial experts were from hospitals, governments, and universities. Hospital experts were exclusively from hospital settings. All company experts were from private companies. Academic experts were from university settings. The auditors

were from hospitals, private companies, governments, and universities. Each group had varying years of experience (Table 1).

The first and second rounds of agreement of experts in the clinical activities of OHS

In the first round of agreement, the experts completed a questionnaire on OHS activities. In the second-round agreement, the experts reconfirmed and modified non-consensus questions. The results of both questionnaires are presented (Table 2). The full statistical results and the final audit tool are provided in the supplementary materials.

Domain 1 – Policy Management: Consensus was achieved on all four activities (100.0%). In the first round, the experts showed strong agreement on the fundamental aspects of policy management, including comprehensive OHS policies, effective communication, policy-aligned activities, and oversight committees. In the second round, consensus was reached on all four key items: company policy covering OHS, policy communication, activity implementation, and the establishment of an oversight committee.

Domain 2 – Fitness for work (FFW) assessment: A consensus was reached in 6 out of the 7 activities (85.7%) including the need for job classification and job-specific examinations, particularly for safety-sensitive positions, with the agreement of the OHP. It was noted that there is also a need for documentation and privacy control of the records. In addition, employee immunization management was included as optional for specific industries, e.g., healthcare, livestock, and food.

Domain 3 – Medical Surveillance: The data showed that all 13 activities (100.0%) reached a consensus regarding the medical surveillance programs being conducted using a hazard-based design by a multidisciplinary team. Surveillance would start with identifying and reviewing the hazards, followed by health risk assessment, regular medical evaluation, followed by interpretation by the OHP. If abnormal results were presented, after the evaluation actions and re-evaluation of the workplace were to be performed.

Domain 4 – Return to Work (RTW) assessment: Consensus was reached for 5 out of the 7 activities, including requirements for RTW indications and OHP evaluation of the relationship between health and work, and suggesting any job alterations or other recommendations as needed. The evaluation should include physical and psychosocial conditions and should establish distinctive management approaches for work-related and non-work-related health conditions.

Domain 5 – Occupational Disease Management: The results showed that a consensus was reached on 8 of 10 activities (80.0%). Those activities focused on employee education regarding health risks, early screening systems, referral programs, and providing information about compensation and benefits as well as management systems for employers, such as the investigation of and reporting systems for occupational diseases.

Domain 6 – Medical Emergency Preparedness: The results demonstrated that consensus was achieved in this domain in 13 out of 15 activities (86.9%). Emergency preparedness requirements covered first-aid protocols and training as well as emergency planning to anticipate all risks, including safety and medical issues. The emergency plan included a referral system, equipment preparation, regular training, and continuous improvement.

Table 1. Demographic data of experts

Expertise groups	Number of experts	Workplace of experts				Years of experience Median (IQR)
		Hospital	Private company	Government sector	University	
Managerial position	6	3	-	1	2	13.5 (8-20)
Hospital-based OHP	7	7	-	-	-	8.0 (7-12)
Company-based OHP	6	-	6	-	-	13.5 (6-35)
Academic OM	6	-	-	-	6	15.5 (8-25)
Auditor	6	1	3	1	1	17.0 (17-20)

OHP, occupational health physicians; OM, occupational medicine

Table 2. Expert agreements on each domains and components of clinical occupational health services audit tool

Occupational health services (OHS) activities	Sum of proportions of level 4 and 5		Consensus
	1st round n = 31 (%)	2nd round n = 31 (%)	
Domain 1 Policy management			
1.1 A company has a policy covering occupational health services	100.0	100.0	Yes
1.2 A company communicates the policy throughout the company	100.0	100.0	Yes
1.3 A company implements and plans activities according to the policy	100.0	100.0	Yes
Domain 2 Fitness for Work Examination (FFW)			
2.1 Employees get FFW examination according to their job titles or similar exposure group (SEG) determined by occupational health physician	96.8	90.3	Yes
2.2 A company has jobs that qualify as safety sensitive job e.g. working in confined space, at heights, driver, or handling toxic, corrosive, or explosive materials that should have fit for work examination	93.6	96.8	Yes
2.3 Occupational health physicians conclude the FFW examination	100.0	100.0	Yes
Domain 3 Medical Surveillance Program			
3.1 The medical surveillance team designs the medical surveillance program according to the result of hazard identification and health risk assessment	100.0	100.0	Yes
3.2 A company performs medical surveillance program regularly according to the health hazard	100.0	100.0	Yes
3.3 Occupational physicians evaluate and interpret the results, correlating them with the exposure	100.0	100.0	Yes
3.4 A company provides medical removal action and follow up examination in employees with abnormal results	96.8	93.6	Yes
Domain 4 Return to work assessment (RTW)			
4.1 A company has documents indicating which conditions, diseases, or injuries to do RTW examination	90.3	87.1	Yes
4.2 A company evaluates individuals based on their health and psychosocial condition, medication, and job demand	96.8	100.0	Yes
4.3 The physicians provide a Return-to-work certification with recommendation of job modification if necessary	100.0	96.8	Yes
4.4 Old – The return-to-work evaluation is done by occupational health physicians, or occupational health doctor, or employees' attending physicians Modify – The return-to-work evaluation can be done by employees' attending physicians but should be re-evaluate by occupational health doctor for the appropriate recommendation	77.4	87.1	Yes
Domain 5 Screening, Diagnosis, and Treatment of occupational diseases			
5.1 A company set a system to trigger a screening for early detection of occupational or work-related diseases	96.8	100.0	Yes
5.2 Old – A company assigns supervisors to be able to detect employees' health condition Modify – Supervisors are aware of the existing health hazard in the workplace	54.8	67.7	No
Domain 6 First aid and medical emergency preparedness			
6.1 A company assigns first-aiders according to the local authorities	96.8	96.8	Yes
6.2 A company trains first-aid practice to supervisors and employees	96.8	90.3	Yes
6.3 A company maintains readiness of the first-aid equipment and facilities	100.0	96.8	Yes
6.4 A company recognizes possible emergencies from workplace health hazards and makes emergency plan accordingly	96.8	100.0	Yes
6.5 A company exercises the emergency plan both discussions based, and operation based	100.0	100.0	Yes
6.6 A company trains Basic life support to employees, annually	67.7	74.2	No
Domain 7 Health promotion			
7.1 The information providers are knowledgeable and qualified to give the information	90.3	100.0	Yes
7.2 A company recognizes the health problems among the employees	93.6	90.3	Yes
7.3 A company provides information about health promotion and wellness including non-occupational injury and illness management	96.8	93.6	Yes

Table 3. Summary of consensus analysis of the audit tool

Domains	Consensus activities n (%)	All activities	Range of consensus on items (median)
1. Policy management	4 (100.0)	4	100-100 (100.0)
2. Fitness for work assessment	6 (85.7)	7	74.2-100 (96.8)
3. Medical surveillance program	13 (100.0)	13	80.7-100 (100.0)
4. Return to work assessment	5 (71.4)	7	64.5-100 (87.1)
5. Occupational diseases management	8 (80.0)	10	61.3-100 (100.0)
6. Medical emergency preparedness	13 (86.9)	15	74.2-100 (96.8)
7. Health promotion	4 (66.7)	6	58.1-100 (85.5)

Domain 7 – Health Promotion: Four out of six activities (66.7%) reached consensus, including the implementation scale of health promotion, recognizing health problems, providing information on health and wellness, evaluating employees, and organizing intervention programs.

In summary, as shown in Table 3, the policy management and medical surveillance program domains achieved the highest consensus, with all activities in these domains reaching 100%, reflecting unanimous agreement among the participants on their importance. Both domains also exhibited a narrow consensus range across individual items, with a median of 100.0%, underscoring consistent prioritization. In contrast, the FFW, occupational disease management, and medical emergency preparedness domains reached consensus levels of 85.7%, 80.0%, and 86.9%, respectively, demonstrating strong agreement but with slightly broader ranges of consensus for individual items. The lowest levels of consensus were observed in the RTW and health promotion domains, with 71.4% and 66.7% consensus, respectively. These findings indicate a more significant variability in the perceived implementation of activities within these domains, as reflected in their broader consensus ranges (median values of 87.1% and 85.5%, respectively). This analysis highlights the variability in consensus across the seven domains, suggesting differing levels of agreement on their criticality and implementation in occupational health.

Additionally, experts offered diverse insights across the seven OHS domains. Overall, there was a strong consensus on the importance of OHP involvement in fitness-for-work evaluations, medical surveillance, and return-to-work processes. Company-based OHPs emphasized the need for context-specific approaches, particularly in policy management and emergency preparedness, reflecting differences in organizational size, resources, and risk profiles. Academics and auditors tended to stress the integration of clinical quality and balanced emphasis on health and safety, while management and company-based OHPs focused more on operational feasibility. Health promotion was widely acknowledged as beneficial, but was consistently recommended only after core protection measures were in place. These perspectives help inform a more nuanced understanding of practical implementation challenges across various occupational settings (Table 4).

DISCUSSION

The modified Delphi technique was used to develop a comprehensive audit tool for evaluating the quality of clinical OHS in corporate settings. While maintaining anonymity and iteration with controlled feedback, the diverse expert panel reached a high level of consensus, supporting the tool's relevance and potential alignment with established practices.

OHS policies differ significantly across countries owing to variations in regulatory frameworks, cultural contexts, and economic conditions. In countries such as the USA (8) and Singapore (10), OHS regulations are well-defined and strictly enforced, focusing on workplace safety and health promotion, including mental health initiatives. In particular, Singapore is notable for integrating occupational health with broader public health systems and promoting wellness alongside traditional safety measures. In contrast, Thailand (26), and the Philippines (27) face challenges in enforcement, with OHS practices primarily concentrated on meeting basic regulatory requirements,

Table 4. Additional comments from experts on each domain

Domains	Management level	Hospital based OHP	Company based OHP	Academics on Occupational Health Sciences	Occupational Health and Safety Auditors
1. Policy Management	Policy/planning must be edited by occupational health services (OHS) team and worker representative before presenting to executives, they may lack the knowledge of the OHS	Internal audit depends on company size/type; more relevant for large hazardous companies	Robust governance from the executives and internal oversight were needed but depending on company resources and understandings from the employer.	Should integrate clinical quality into holistic control	Audit should be equitable in all areas, the OHS should have equal weightage to safety and the boards should be aware of the importance of the OHS
2. Fit for work assessment	occupational health physicians (OHP) should be the one to do Fitness for work (FFW)	Functional capacity evaluation (FCE) only for impaired employees in safety-sensitive jobs	FFW must be risk-based and job-specific; no one-size-fits-all tests	FCE can be outsourced, or could consider trade tests as FCE alternative	FCE/trade tests were important for objective assessment
3. Medical Surveillance Program	Special exams must include specific diagnostics based on worker histories	Design team must include OHP (in-house/external) and the procedure should be written clearly	OHP should work with organization representatives for understanding hazards and the implementation of the program	Can outsource to third party but must include OHP	OHP and safety officer were needed to design the program
4. Return to work assessment	Company should assist unfit employees to transfer to appropriate work; by having discussions between employer, employee, and the OHP	Return to work (RTW) should be done by OHP, early return to work can best benefit the worker	Need clear policy for RTW and different handling for work vs non-work conditions, the work adaptation should be done to shorten lost workdays	No specific comment provided	Must be handled by trained personnel or OHP considering company policies
5. Occupational diseases management	All top management should be aware of workplace health hazards and exposure risks	No specific comment provided	Supervisors should identify concerning behaviours, not diagnosing conditions	Can use general screening questionnaire in screening or follow local guidelines	Medical personnel should evaluate health, not supervisors
6. Emergency preparedness	Need specific details on facility accessibility, considering distance/time and clinical guidelines for golden period	No specific comment provided	Response guarantees should not be set, it can be varied by company hazards/size	Transport can be outsourced; consider limitations for small enterprises	Employer should decide provisions based on multiple factors e.g. hazards, safety risks
7. Health Promotion	It is a primary prevention; align with Universal Health Care, but it should be done after satisfying all core workers protection.	It is a preventive service; it can include only company-controlled aspects	Promoting health and lifestyle can benefit on productivity and financial returns	Health promotion is a part of basic OH	Health promotion is a part of prevention and can improve productivity

which are often limited to physical safety and medical surveillance, without addressing broader health promotion or mental well-being issues.

In addition, across the seven domains covered by the tool, consensus was achieved on 53 of 62 individual audit activities, with agreement exceeding 80.0% in each case. This strong consensus underscores the validity of the tool and its concordance with established OHS guidelines of leading organizations, including the ILO Conventions and Recommendations (28, 29), the American Medical Association (30), and the WHO (31).

The experts reached unanimous consensus (100.0%) in the policy management domain. The results showed three critical activities that scored 100% agreement in both rounds: policy establishment, communication throughout the organization, and systematic implementation of activities. Employers must provide OHS (28) and management-level and company-based OHP experts advocated executive involvement in policy development. However, they also commented on executives' lack of expertise and understanding of OHS, highlighting the need for leadership-level education and training. This was evidenced by a study of Japanese companies, where only 12 out of 267 responding companies fully integrated occupational health elements into their OSHMS, with over 50.0% of companies which were planning implementation being uncertain about how to incorporate occupational health activities, demonstrating a significant knowledge gap at the management level (32). In addition, hospital-based experts recommended scaling requirements based on the company size and hazard levels. Lau et al. (33) demonstrated how standardized policies might not effectively account for varying operational capacities and clinical demands across healthcare settings.

In examining the second domain, FFW assessment, an 85.7% consensus was reached, establishing crucial requirements for job-specific examinations. The experts agreed on three key elements: examination protocols based on job titles or similar exposure groups; special attention to safety-sensitive positions, e.g., confined spaces, heights, driving, or handling hazardous materials (34); and oversight by occupational health physicians. The consensus in this domain emphasized the critical role of occupational health physicians including FFW examinations. As supported by the ACOEM's core competency of OHP, OHP should have the knowledge and skills to determine whether workers can safely be at work and perform the required job tasks (35).

Medical surveillance revealed the highest consensus (100.0%) among the panelists. The core requirements outlined in the tool were hazard-based program design, regular monitoring, and OHP result interpretation. Surveillance is a key indicator of exposure control effectiveness and triggers early intervention, thereby reducing the burden of occupational illness. This was demonstrated in both the reviewed studies. Mandanach's analysis showed how effective surveillance enabled the monitoring of occupational disease prevalence and the adoption of preventive measures (36).

In contrast, Sen et al.'s comparative analysis revealed that countries with robust surveillance systems were better able to identify high-risk areas and implement targeted prevention programs, ultimately reducing the occupational disease burden through early intervention (37). Moreover, expert consensus on effective medical surveillance requires close collaboration between occupational health professionals and safety specialists. As Murthy emphasized, maintaining a safe and healthy workplace requires integrated expertise from all occupational health domains, including industrial hygienists, safety officers, occupational health nurses, and practicing physicians (38).

The fourth domain, RTW assessment, reached a 71.4% consensus, reflecting divergence in implementation approaches. The agreed components included documentation of qualifying conditions, comprehensive individual evaluation considering health and psychosocial factors, and physician certification with modification recommendations. The experts emphasized the need for OHP recommendations to ensure that the workplace context was adequately considered. This collaborative approach aligns with the research by Tan et al., who demonstrated through case evidence that a successful return to work requires careful evaluation of functional impairment against job demands and workplace capabilities (39). Additionally, Nastasia et al. found that even in resource-limited settings, such as SMEs, early return with informal but monitored task modifications could

be effective when adequately supported by occupational health professionals, leading to better outcomes and faster recoveries (40). Both studies reinforced the experts' view that OHPs are crucial in bridging the gap between medical care, workplace capabilities, and worker needs during the return-to-work process.

Occupational disease management achieved an 80.0% consensus, focusing on two core elements: implementing early detection systems and enhancing workplace hazard awareness. Based on the established legal principles outlined by Henshaw et al., employers bear the primary responsibility for worker protection because they control work methods and conditions (41). Griffin noted that this requires management and supervisor training to recognize work-related illness signs to help ensure prompt response and impact mitigation (42). The expert panelists emphasized that integrating these elements with regulatory compliance and voluntary prevention measures was critical for program success.

Medical emergency preparedness showed a strong consensus (86.9%) across five key areas: first-aid assignment, training programs, equipment maintenance, emergency planning, and exercise programs. Experts also commented on the need for flexibility in setting response time standards based on the specific hazards present and the accessibility of emergency medical services. These practices emphasize the importance of a well-rehearsed and adaptable emergency response capability. According to a systematic review by Dagrenat et al., workplace first-aid practices and standards showed significant variations in regulation, organization, and training requirements. These differences highlight the need for emergency response capabilities that adapt to local contexts while maintaining core training standards. That study found that despite the universal recognition of the importance of workplace first aid, countries lacked uniform recommendations, enabling flexible implementation (43).

Health promotion received the lowest consensus among the domains evaluated (66.7%), despite expert acknowledgment of its significance in disease prevention and productivity enhancement. Some management-level respondents advocated prioritizing traditional occupational health protection over health promotion. This perspective aligns with the hierarchical framework of occupational health services (OHS) proposed by Guidotti et al., who conceptualized health promotion as an extension of the basic occupational medical care (30). Emerging frameworks, such as the Total Worker Health (TWH) approach developed by the National Institute for Occupational Safety and Health (NIOSH), advocate the integration of health protection and promotion. The TWH model emphasizes that comprehensive strategies are essential for optimizing worker well-being. Incorporating these elements into OHS reduces healthcare expenditures and enhances overall employee productivity and quality of life within and beyond the workplace (44).

This systematic approach to clinical occupational health service audits fills significant gaps in existing standards, such as SEQOHS (14), ACOEM (15), and WHO guidelines (31), particularly in addressing detailed clinical quality metrics. It also serves as a practical instrument for organizations to ensure compliance with Thailand's ministerial regulation on employee health examinations (12). The tool provides practical guidance and supports continuous quality improvement in OHS delivery.

Strengths and limitations

The strength of this study lies in its comprehensive coverage of seven key domains of clinical OHS, offering a comprehensive approach to evaluating and improving service delivery. A strong consensus (80.0% agreement) on essential activities across these domains further validates the tool's reliability. Additionally, the tool emphasizes continuous quality improvement, providing a structured framework for organizations to assess and refine their OHS practices over time.

A limitation of the study was that it focused primarily on organizational settings but was not suitable for informal workers' settings. Additionally, cultural and regional variations in occupational health practices may not be fully represented. This tool may require significant adaptation to different national regulatory contexts. Moreover, the study did not include field testing of the audit tool in a real-world setting. Therefore, audit tools should be pretested and modified according to the country's practices.

Recommendations

Companies can use the audit tool to help provide a quality OHS to their employees. These implications extend to service delivery, management approaches, and potential outcomes for holistic employee healthcare. This tool can serve as a basis for developing or enhancing OHS programs and facilitating dialogue between management, health professionals, and workers. The tool is designed to be flexible, allowing for adaptation to different organizational contexts and sizes. This tool enables organizations to identify strengths and gaps in their clinical occupational health services, promote consistency in service delivery, and support continuous quality improvement. A phased implementation approach is recommended, starting with the core activities that reached a high level of consensus.

CONCLUSIONS

Clinical OHS audit tools may include 7 domains: policy management, medical assessment for FFW, medical surveillance programs, medical assessment for RTW, occupational disease management, medical emergency preparedness, and health promotion. These domains established a comprehensive framework including valuable insights from experts from diverse professional backgrounds and OHS settings. This diversity of perspectives contributes to a more robust and practical audit tool that balances ideal practices with real-world implementation possibilities.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

The data supporting the findings of this study are available within the article and its supplementary materials.

Supplementary materials

The following supporting information can be downloaded at: Supplementary appendix

REFERENCES

1. International Labour Organization. A call for safer and healthier working environments. ILO (Internet). 2023 (cited 2025 Jan 12). Available from: https://researchrepository. ilo.org/esploro/outputs/report/995343988202676
2. British Standards Institution. BS 8800: guide to occupational health and safety management systems. London: The Institution; 1996.
3. British Standards Institution. OHSAS 18001:2007 Occupational health and safety management systems - requirements. London: The Institution; 2007.
4. International Organization for Standardization. ISO 45001:2018 - Occupational health and safety management systems - requirements with guidance for use. Geneva: The Organization; 2018.
5. Caponecchia C, Wyatt A. Defining a "safe system of work." Saf Health Work. 2021;12(4):421–3.
6. World Health Organization, International Labour Organization. WHO/ILO joint estimates of the work-related burden of disease and injury, 2000-2016: global monitoring report. (Internet). Geneva: World Health Organization; 2021 Sep (cited 2023 Apr 20). Available from: https://www.who.int/publications-detail-redirect/9789240034945
7. Rantanen J. Occupational health services: an overview. Copenhagen: World Health Organization Regional Office for Europe; 1990.
8. Occupational Safety and Health Act of 1970, Pub. L. No. 91-596, 84 Stat. 1590 (Dec. 29, 1970) (Internet). Washington, DC: United States Department of Labor; 1970 (cited 2023 Apr 18). Available from: https://www.osha.gov/laws-regs/oshact/completeoshact
9. Health and Safety at Work Act 1974, c. 37 (UK). London: Her Majesty's Stationery Office; 1974.
10. Ministry of Manpower. Workplace Safety and Health Act 2006. Singapore; 2006.
11. Department of Occupational Safety and Health Malaysia. Occupational Safety and Health Act of 1994. Malaysia: DOSH; 1994.
12. Royal Thai Government Gazette. Ministerial Regulation on the Prescribing of Standards for Services of Occupational Health Units B.E. 2567 (A.D. 2024). Sect. Pt 73 k Nov 25, 2024 p. 38-46.
13. Tang KHD. A comparative overview of the primary Southeast Asian safety and health laws. IJWHM 2020; 13:601-32.

14. Standards for safe effective quality occupational health service (SEQOHS) (Internet). London: Faculty of Occupational Medicine; 2023 (cited 2024 Apr 23). Available from: https://www.seqohs.org/CMS/Page.aspx?PageId=77
15. American College of Occupational and Environmental Medicine. Guide to the health, safety and environmental management (HSEM) system. Elk Grove Village (IL): The College; 2005.
16. Pokkapat Prasatkettkarn. Enterprises' expectation on competencies of occupational physicians and occupational health administration in Thailand. Dis Control J. 2022;48:626-36.
17. Cashman C. A survey of current audit practice in occupational health. Occup Med. 2019;69:287–9.
18. Lalloo D, Demou E, Macdonald EB. Impact of peer review audit on occupational health report quality. Occup Med. 2015;65:440–3.
19. Rahman MS. The advantages and disadvantages of using qualitative and quantitative approaches and methods in language "testing and assessment" research: a literature review. J Educ Learn. 2016;6:102-12.
20. Michalak J. Quality assessment in occupational health services: a review. Int J Occup Med Environ Health. 2002;15:165-71.
21. Bilban M. Quality assurance in occupational medicine. Saf Eng. 2014;4:17-24.
22. Meesil N. Delphi technique: avoidance of misconception. Veridian E-Journal Silpakorn Univ Humanit Soc Sci Arts. 2016;9:1256–67.
23. Von Der Gracht HA. Consensus measurement in Delphi studies. Technol Forecast Soc Change. 2012;79:1525–36.
24. Macmillian TT. The Delphi technique. Paper presented at the annual meeting of the California Junior Colleges Associations Committee on Research and Development; 1971 May 3-5; Monterey; 1971.
25. Ismail FKM, Zubairi AMB. Item objective congruence analysis for multidimensional items content validation of a reading test in Sri Lankan university. Engl Lang Teach. 2022;15:106-17.
26. Royal Thai Government Gazette. Occupational health and safety and environment Act B.E. 2554 (A.D. 2011). Sect. Pt 4 k Jan 17, 2011 p. 5-25.
27. Republic of the Philippines. Republic Act No. 11058: An Act strengthening compliance with occupational safety and health standards and providing penalties for violation thereof. Quezon City: Republic of the Philippines; 2018.
28. International Labour Organization. Convention No. 161 concerning occupational health services. Geneva: The Organization; 1985.
29. International Labour Organization. Recommendation No. 171 concerning occupational health services. Geneva: The Organization; 1985.
30. Guidotti TL. The occupational health care system. In: Guidotti TL. Occupational health services: a practical approach. 2nd ed. Oxon: Routledge/Taylor & Francis Group; 2013. p. 1-17
31. World Health Organization Regional Office for Europe. Good practice in occupational health services: a contribution to workplace health. Copenhagen: The Organization; 2002.
32. Ikeda Y, Kameda T, Shirakawa C, Nagata T, Zama S, Kayashima K, et al. The relation among expertise level of occupational health physician, implementation of occupational safety and health management system (OSHMS) and occupational safety and health activity level in Japan in the companies listed on Tokyo stock exchange first section. J UOEH. 2007;29:469-84.
33. Lau B, Miguel SS, Chow J. Policy and clinical practice: audit tools to measure adherence. Ren Soc Australas J. 2010;6:36-40.
34. Lee LP, Martin DW, Kancelbaum B, Israel M, Reid N, Pick TA, Schumann SC, Thies RE. Occupational medicine: a basic guide. A publication of the ACOEM private practice section [DRAFT]. Elk Grove Village: ACOEM; 2018.
35. Hartenbaum NP, Baker BA, Levin JL, Saito K, Sayeed Y, Green-McKenzie J. ACOEM OEM core competencies: 2021. J Occup Environ Med. 2021;63:e445–61.
36. Mandanach C. Patterns in medical surveillance of workers exposed to lung carcinogens. RJOM. 2023;74:23-9.
37. Şen S, Barlas G, Yakıştıran S, Derin İG, Şerifi BA, Özlü A, et al. Prevention of occupational diseases in Turkey: deriving lessons from journey of surveillance. Saf Health Work. 2019;10:420-7.
38. Murthy LI. Implementing workplace safety and health surveillance. Ann N Y Acad Sci. 1997;837(1):100-104.
39. Tan KWA, Koh D. Long COVID—Challenges in diagnosis and managing return-to-work. J Occup Health. 2023;65(1):e12401. PubMed PMID: 37098838
40. Nastasia I, Coutu MF, Lederer V, Lecours A, Rives R. Insights into small and medium enterprises practices of early return to work with modified tasks following a work-related injury [Abstract]. Occup Med. 2024;74(Supplement_1):i339.
41. Henshaw JL, Gaffney SH, Madl AK, Paustenbach DJ. The employer's responsibility to maintain a safe and healthful work environment: an historical review of societal expectations and industrial practices. Empl Responsib Rights J. 2007;19:173-92.
42. Griffin MJ. Negligent exposures to hand-transmitted vibration. Int Arch Occup Environ Health. 2008;81:645-59.
43. Dagrenat C, Cassan P, Issard D, Loeb T, Baer M, Descatha A. 541 First aid in the workplace in the world: a systematic review. Occup Environ Med. 2018;75(Suppl_2):A114.
44. National Institute for Occupational Safety and Health (NIOSH). Fundamentals of Total Worker Health approaches: essential elements for advancing worker safety, health, and well-being. Cincinnati (OH): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, NIOSH; 2016. DHHS (NIOSH) Publication No. 2017-112.

Audit tool – Prototype

This audit tool aims to evaluate the clinical part of occupational health services provided in companies. It can be used as a recommendation or a guideline in operating occupational health services. However, the need to comply with local authorities is still needed as a fundamental practice. [Evaluation- Yes/No]

Occupational health services activities

OHS activities		Evaluation
Domain 1 Policy management		
1.1	A company has a policy covering occupational health services	
1.2	A company communicates the policy throughout the company	
1.3	A company implements and plans activities according to the policy	
1.4	A company has a committee overseeing the implementation of the policy	
Domain 2 Fit for Work examination (FFW)		
2.1	Employees get FFW examination according to their job titles or similar exposure group (SEG) determined by occupational health physician	
2.2	A company has jobs that qualify as safety sensitive job e.g. working in confined space, at heights, driver, or handling toxic, corrosive, or explosive materials that should have fit for work examination	
2.3	Occupational health physicians conclude the FFW examination	
2.4	A company shows evidence of a system for employees' health record keeping including informed consent from employees and accessibility control of the records	
2.5	A company documents FFW examinations results and keeps them individually for further reference	
Optional for this domain		
2.6	A company requires specific testing, e.g. functional capacity evaluations (FCE) or trade test, to evaluate employees in the safety sensitive job	
2.7	A company reviews immunization status and provides prophylaxis vaccination for employees (health services, food industry, or livestock industry)	
Domain 3 Medical Surveillance Program		
3.1	A company shows evidence of a mechanism process to get hazard identification and health risk assessment	
3.2	A company reviews all the information from the safety data sheet and industrial hygiene data	

OHS activities	Evaluation
3.3 The medical surveillance team designs the medical surveillance program according to the result of hazard identification and health risk assessment	
3.4 A company performs medical surveillance program regularly according to the health hazard	
3.5 A company performs the medical examination in an appropriate location	
3.6 Occupational physicians evaluate and interpret the results, correlating them with the exposure	
3.7 A company reports the results to the employees	
3.8 A company provides reconfirmation and diagnosis to employees with abnormal results	
3.9 A company provides medical removal action and follow up examination in employees with abnormal results	
3.10 A company reevaluates work environment and control measures	
3.11 A company makes changes by hierarchy of control according to the information from the evaluation (from 3.10)	
3.12 A company documents and keeps the examination results according to their health hazard exposure group for further reference	
3.13 A company has a medical surveillance design team which should include at least: 1) human resources or safety officers, 2) occupational health professionals, and 3) supervisors	
Domain 4 Return to work assessment (RTW)	
4.1 A company has documents indicating which conditions, diseases, or injuries to do RTW examination	
4.2 A company evaluates individuals based on their health and psychosocial condition, medication, and job demand	
4.3 The return-to-work evaluation is done based on scientific/relevant organization guidelines (e.g. AMA)	
4.4 The physicians provide a Return-to-work certification with recommendation of job modification if necessary	
4.5 The return-to-work evaluation can be done by employees' attending physicians but should be re-evaluated by occupational health doctor for the appropriate recommendation	
4.6 A company attempts to alter the job based on recommendations, and the supervisors and safety officers are aware of the need and make the changes as practical and appropriate as possible.	
4.7 A company advices and assists on compensation and vocational rehabilitation for employees who are unfit to work	
Domain 5 Occupational diseases management	
5.1 A company educates employees about their hazards and possible health risks and how to prevent and manage the risks	

OHS activities	Evaluation
5.2 A company set a system to trigger a screening for early detection of occupational or work-related diseases	
5.3 A company has a referral program to the specialist for employees with occupational diseases or injuries	
5.4 A company documents the referral	
5.5 A company provides information about compensation, or disabilities benefits to the employees	
5.6 A company provides an investigation report of occupational disease or injuries	
5.7 A company uses the investigation report to propose actions and act accordingly with follow-up inspection and evaluation of the changes	
5.8 A company reports cases in compliance with the local regulations	
5.9 A company has general screening questionnaires for screening and early detection of occupational diseases	
5.10 Supervisors are aware of the existing health hazard in the workplace	
Domain 6 First aid and medical emergency preparedness	
6.1 A company assigns first-aiders according to the local authorities	
6.2 A company trains first-aid practice to supervisors and employees	
6.3 The BLS trainers are qualified or certified for first-aid training	
6.4 A company observes and documents or records the training session, results, and evaluation of the first-aid training	
6.5 A company maintains readiness of the first-aid equipment and facilities	
6.6 A company has a referral system for emergency condition	
6.7 A company provides medical forms and contact people for referral system	
6.8 A company provides transportation with capabilities of transferring patients	
6.9 A company recognizes possible emergencies from workplace health hazards and make emergency plan accordingly	
6.10 A company provides appropriate PPE and treatment for the anticipated medical emergency	
6.11 A company assigns roles of Incident Command System and Emergency Operation Center to employers and employees	
6.12 A company exercises the emergency plan both discussions based, and operation based	
6.13 A company discusses and makes improvement of the plan after the exercise	
6.14 A company trains Basic life support to employees, annually	
6.15 A company has prepared a process of transferring emergency patients promptly.	

OHS activities	Evaluation
Domain 7. Health promotion	
7.1 The information providers are knowledgeable and qualified to give the information	
7.2 A company recognizes the health problems among the employees	
7.3. A company provides information about health promotion and wellness including non-occupational injury and illness management	
7.4 A company provides health promotion based on employees age group and common problems	
7.5 A company has intervention program to support employees' behavior changes	
7.6 A company evaluates employees after the program	

Statistical Results and Consensus Analysis of each item

Occupational health services activities

OHS activities	1st round	2nd round	Consensus
Domain 1 Policy management			
1.1 A company has a policy covering occupational health services	100	100	Yes
1.2 A company communicates the policy throughout the company	100	100	Yes
1.3 A company implements and plans activities according to the policy	100	100	Yes
1.4 A company has a committee overseeing the implementation of the policy	96.8	100	Yes
Domain 2 Fit for Work examination (FFW)			
2.1 Employees get FFW examination according to their job titles or similar exposure group (SEG) determined by occupational health physician	96.8	90.3	Yes
2.2 A company has jobs that qualify as safety sensitive job e.g. working in confined space, at heights, driver, or handling toxic, corrosive, or explosive materials that should have fit for work examination	93.6	96.8	Yes
2.3 Occupational health physicians conclude the FFW examination	100	100	Yes
2.4 A company shows evidence of a system for employees' health record keeping including informed consent from employees and accessibility control of the records	96.8	100	Yes
2.5 A company documents FFW examinations results and keeps them individually for further reference	96.8	100	Yes
2.6 Old – A company has special tests or functional capacity evaluations to evaluate the employees in the safety sensitive job Modify – A company requires specific testing, e.g. functional capacity evaluations (FCE) or trade test, to evaluate employees in the safety sensitive job	58.1	74.2	No
2.7 Old – A company reviews employee's immunization status (optional, used in company that requires immunization e.g. health services, food industry, or livestock industry) Old – A company provides fundamental and prophylaxis vaccinations to the non-immune employees (optional, used in company that requires immunization e.g. health services, food industry, or livestock industry)	77.4 74.2	96.8	Yes

OHS activities	1st round	2nd round	Consensus
Modify – Optional, a company reviews immunization status and provides prophylaxis vaccination for employees (health services, food industry, or livestock industry)			
Domain 3 Medical Surveillance Program			
3.1 A company shows evidence of a mechanism process to get hazard identification and health risk assessment	93.6	100	Yes
3.2 A company reviews all the information from the safety data sheet and industrial hygiene data	100	96.8	Yes
3.3 The medical surveillance team designs the medical surveillance program according to the result of hazard identification and health risk assessment	100	100	Yes
3.4 A company performs medical surveillance program regularly according to the health hazard	100	100	Yes
3.5 A company performs the medical examination in an appropriate location	96.8	100	Yes
3.6 Occupational physicians evaluate and interpret the results, correlating them with the exposure	100	100	Yes
3.7 A company reports the results to the employees	96.8	100	Yes
3.8 A company provides reconfirmation and diagnosis to employees with abnormal results	96.8	87.1	Yes
3.9 A company provides medical removal action and follow up examination in employees with abnormal results	96.8	93.6	Yes
3.10 A company reevaluates work environment and control measures	100	100	Yes
3.11 A company makes changes by hierarchy of control according to the information from the evaluation (from 3.10)	100	100	Yes
3.12 A company documents and keeps the examination results according to their health hazard exposure group for further reference	100	96.8	Yes
3.13 Old – A company has a team in designing the medical surveillance program Old – the team members consist of safety officer and occupational health professionals and industrial hygienist and production team representatives Modify – A company has a medical surveillance design team which should include at least: 1) human resources or safety officers, 2) occupational health professionals, and 3) supervisors	74.2 71.0	80.7	Yes

OHS activities		1st round	2nd round	Consensus
Domain 4 Return to work assessment (RTW)				
4.1	A company has documents indicating which conditions, diseases, or injuries to do RTW examination	90.3	87.1	Yes
4.2	A company evaluates individuals based on their health and psychosocial condition, medication, and job demand	96.8	100	Yes
4.3	The return-to-work evaluation is done based on scientific/relevant organization guidelines (e.g. AMA)	100	100	Yes
4.4	The physicians provide a Return-to-work certification with recommendation of job modification if necessary	100	96.8	Yes
4.5	Old – The return-to-work evaluation is done by occupational health physicians, or occupational health doctor, or employees' attending physicians Modify – The return-to-work evaluation can be done by employees' attending physicians but should be re-evaluate by occupational health doctor for the appropriate recommendation	77.4	87.1	Yes
4.6	Old – A company alters the job based on the recommendation Old – A company provides supervisor feedback after the job modification Modify –A company attempts to alter the job based on recommendations, and the supervisors and safety officers are aware of the need and make the changes as practical and appropriate as possible.	71.0 79.0	74.2	No
4.7	Old – A company provides information about vocational rehabilitation for employees unfit to work Old – A company provides information about compensation for employees who are unfit to work Modify – A company advice and assists on compensation and vocational rehabilitation for employee who are unfit to work	64.5 74.2	64.5	No
Domain 5 Screening, Diagnosis, and Treatment of occupational diseases				
5.1	A company educates employees about their hazards and possible health risks and how to prevent and manage the risks	96.8	100	Yes
5.2	A company set a system to trigger a screening for early detection of occupational or work-related diseases	96.8	100	Yes

OHS activities	1st round	2nd round	Consensus
5.3 A company has a referral program to the specialist for employees with occupational diseases or injuries	96.8	100	Yes
5.4 A company documents the referral	96.8	100	Yes
5.5 A company provides information about compensation, or disabilities benefits to the employees	100	100	Yes
5.6 A company provides an investigation report of occupational disease or injuries	100	100	Yes
5.7 The investigation report proposes preventive actions From previous activities, a company manages or changes according to the proposal From previous activities, a company has a follow-up inspection and evaluation of the changes Combining above activities A company uses the investigation report to propose actions and act accordingly with follow-up inspection and evaluation of the changes	100 100 100	96.8	Yes
5.8 A company reports cases in compliance with the local regulations	96.8	93.6	Yes
5.9 Old – A company has specific tests or questionnaires for screening and early detection for occupational diseases Old – A company has specific questionnaires for screening for specific hazard such as asbestos, lead, silica, pesticides, or confined space Modify – A company has general screening questionnaires for screening and early detection of occupational diseases	67.7 77.4	61.3	No
5.10 Old – A company assigns supervisors to be able to detect employees' health condition Modify – Supervisors are aware of the existing health hazard in the workplace	54.8	67.7	No
Domain 6 First aid and medical emergency preparedness			
6.1 A company assigns first-aiders according to the local authorities	96.8	96.8	Yes
6.2 A company trains first-aid practice to supervisors and employees	96.8	90.3	Yes
6.3 The BLS trainers are qualified or certified for first-aid training	100	96.8	Yes
6.4 A company observes and documents or records the training session, results, and evaluation of the first-aid training	100	96.8	Yes
6.5 A company maintains readiness of the first-aid equipment and facilities	100	96.8	Yes

OHS activities	1st round	2nd round	Consensus
6.6 A company has a referral system for emergency condition	100	100	Yes
6.7 A company provides medical forms and contact person for referral system	100	100	Yes
6.8 A company provides transportation with capabilities of transferring patients	93.6	93.6	Yes
6.9 A company recognizes possible emergencies from workplace health hazards and makes emergency plan accordingly	96.8	100	Yes
6.10 A company provides appropriate PPE and treatment for the anticipated medical emergency	100	100	Yes
6.11 A company assigns roles of Incident Command System and Emergency Operation Center to employers and employees	100	100	Yes
6.12 A company exercises the emergency plan both discussions based, and operation based	100	100	Yes
6.13 A company discusses and makes improvement of the plan after the exercise	100	100	Yes
6.14 A company trains Basic life support to employees, annually	67.7	74.2	No
6.15 Old – The available healthcare service is located within 10 Kms. Old – A company can transfer patients to the available healthcare service within 10 minutes Modify –A company sets guarantee duration for emergency conditions and can practice accordingly	58.1 61.3	77.4	No
Domain 7. Health promotion			
7.1 The information providers are knowledgeable and qualified to give the information	90.3	100	Yes
7.2 A company recognizes the health problems among the employees	93.6	90.3	Yes
7.3. A company provides information about health promotion and wellness including non-occupational injury and illness management	96.8	93.6	Yes
7.4 A company provides health promotion based on employees age group and common problems	90.3	80.7	Yes
7.5 A company evaluates employees after the program	74.2	58.1	No
7.6 A company has an intervention program to support employees' behavior changes	77.4	64.5	No

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Original Article

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Investigating the Role of Genetic Polymorphism in the Exon 3 of ATG16L1 Gene in T2DM Patients: A Pilot Study

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ABSTRACT

OBJECTIVE Diabetes mellitus (DM) is a metabolic disease characterized by persistently high blood sugar levels and has several potential causes. We aimed to find out whether there are any single nucleotide polymorphisms in a particular region of the *ATG16L1* gene which are linked to type 2 diabetes.

METHODS A total of forty participants were included in this study; 20 were part of the patient group and had type 2 diabetes mellitus (T2DM), while 20 were part of the healthy control group. High-resolution melt (HRM) analysis was used for genotyping along with sequencing for confirmation of the results.

RESULTS The melting behavior showed consistent DNA sequence in the exon 3 of the *ATG16L1* gene in both the patient and the healthy control groups in the study.

CONCLUSIONS The *ATG16L1* gene does not include any SNPs in the exon 3 region associated with type 2 diabetes. However, further studies are needed to determine the role of the autophagy gene in T2DM.

KEYWORDS ATG16L1, HRM, SNP, T2DM, autophagy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a widespread metabolic disease characterized by the failure of insulin-responsive cells to respond to insulin or to the insufficient secretion of insulin by insulin-producing cells. During the disease, insulin secretion becomes inadequate for glucose regulation, resulting in hyperglycemia, the hallmark of T2DM (1). There is mounting evidence that genetic factors play a role in susceptibility to type 2 diabetes (2, 3). Autophagy is a cellular process that eliminates and recycles damaged cellular components. The *ATG16L1* gene encodes the ATG16L1 protein, which is essential for this activity (4). Along with its function in autophagy, ATG16L1 also controls the immunological response, intracellular trafficking, and inflammation (5).

The *ATG16L1* gene is essential for the autophagic process in pancreatic β-cells, which is vital for insulin release and β-cell functionality. (6). People with diabetes, especially type 2 diabetes, commonly experience higher levels of oxidative stress and endoplasmic reticulum stress in their β-cells, which can be managed by autophagy, a defensive process that cells employ (7). Autophagy ensures the well-being of β-cells in diabetes by eliminating damaged organelles and misfolded proteins. However, β-cell failure and the advancement of diabetes are caused by dysregulated autophagy, which is observed in diabetic circum-

stances (8). Several autophagy proteins, including ATG16L1, govern autophagosome production, which degrades and recycles cellular components (9). β-cells in T2DM patients have impaired autophagy resulting in the accumulation of toxic proteins, which induces endoplasmic reticulum stress and diminishes β-cell function, thereby exacerbating insulin resistance and elevated blood glucose levels (10, 11). This study aimed to investigate specific genetic markers in the selected region on the *ATG16L1* gene that may be associated with type 2 diabetes.

METHODS

Subjects. The pilot study consisted of 40 participants in total, 20 individuals with T2DM in the patient group, and the same number in the healthy control group. Diabetic status was determined using standards set by the World Health Organization (12, 13) and based on reports by the patients' endocrinologists. Patients with either type 1 diabetes or other chronic diseases were excluded from the study. The control group included healthy individuals with no history of diabetes or related metabolic disorders. They were recruited from Al-Sader Teaching Hospital, Najaf, Iraq. Before blood collection, we ensured that patients' informed consent was obtained.

Ethical approval for conducting this study was obtained from the College of Medical Technology, the Islamic University in Najaf (No. 40, 1/6/2024).

The study was carried out in the molecular laboratories at the Al-Furat Al-Awsat Technical University and the Islamic University, Najaf, Iraq. Both groups underwent similar testing procedures, including the collection of blood samples for genetic and biochemical analysis.

Pre-genotyping. DNA was extracted from whole blood samples following the manufacturer's protocol (iNtRON Biotechnology, Seongnam, Korea) as in our previous studies (12, 14). The primers for PCR were prepared using the standard method for dilution of stock primers to concentrations of 10 µM.

Genotyping. The Rotor-Gene Q RT-PCR system (Qiagen, Hilden, Germany) was employed to carry out high-resolution melt (HRM) analysis using real-time PCR. Following the instructions of the kit, 5 µL of DNA was mixed with 10 µL of GoTaq® qPCR master mix (Promega), and one µl each of forward and reverse primers (10 µM) was subsequently introduced into the mixture. The final volume was then adjusted to 20 µL. The PCR program was conducted as follows. The mixture was preheated to 95°C. Then 40 cycles of the run, each consisting of three steps (denaturation at 95 °C/25 S, annealing at 58 °C/40 S, and elongation at 72 °C/35 S), were conducted. Primer sequences are listed in Table 1. After amplification, the PCR products were subjected to gradual melting from 60° to 95 °C at a ramp rate of 0.1 °C per second as described in our previous study (14). The melting curves were analyzed using the Rotor-Gene Q-Pure Detection software (Qiagen, Hilden, Germany).

Statistical analysis. The GraphPad Prism program version 9 for Mac (San Diego, CA, USA) was used to perform the statistical analysis, using chi-square and student's t-test. Qualitative data are shown as frequencies. The alignment of the sequencing data was performed using Geneious Prime software (Biomatters Ltd., Auckland, New Zealand). The analysis of the melting curves was carried out with the assistance of the Rotor-Gene Q-Pure Detection program.

RESULTS

The characteristics of the participants in the study are summarized in Table 2. The mean age of the control group was 42.75 and of the study group was 54.90. The mean duration of diabetes was 6.733 years and the average body mass index was 25.95 Kg/m^2 in the control and 29.71 Kg/m^2 in the patient group. Random blood sugar (RBS)

Table 1. Primer sequences of exon 3 of the *ATG16L1* gene

Primer direction	Primer sequence	Tm	Annealing temperature	Amplicon (bp)
Forward	CTTCATCTGCCTGGTTTGCC	60	58 °C	135
Reverse	ACCTCCCCACGTTTCTTGTG	60		

Table 2. Characteristics of patient and control groups in the study

Characteristics	Control (n=20)	Patient (n= 20)	*p*-value
Age	42.75 (13.67)	54.90 (13.11)	0.0067
Sex; N (%)			
Male	10 (50.00)	11 (55.00)	0.7520
Female	10 (50.00)	9 (45.00)	
Duration of diabetes (years)		6.733 (7.35)	
Height (m)	174.4 (10.09)	170.1 (11.55)	0.1040
Weight (Kg)	75.40 (14.98)	80.50 (20.63)	0.3770
BMI (Kg/m^2)	25.95 (4.65)	29.71 (6.31)	0.0386
RBS (mg/dL)	99.80 (16.90)	183.0 (64.64)	< 0.0001
HbA1c (%)	5.11 (0.58)	8.00 (2.253)	< 0.0001

BMI, body mass index; RBS, random blood sugar

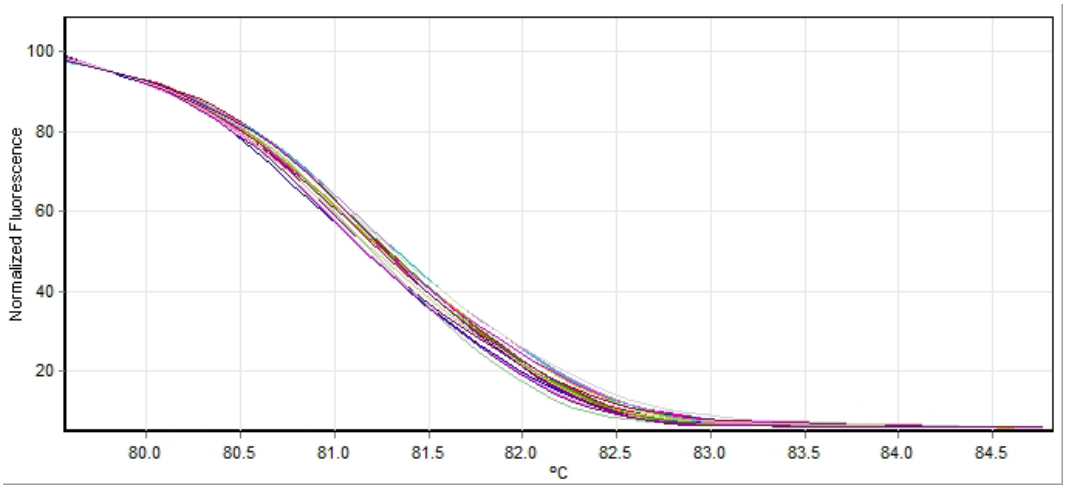

Figure 1. Normalized HRM PCR plot

and HbA1c levels were significantly elevated in the patient group. The mean RBS in the patient group was 183.0 mg/dL (SD 64.64) compared to 99.80 mg/dL (SD 16.90) in the control group ($p < 0.0001$). Similarly, HbA1c levels were significantly higher in the patient group, with a mean of 8.00% (SD 2.253) compared to 5.11% (SD 0.58) in the control group ($p < 0.0001$).

The region of exon 3 of the *ATG16L1* gene was explored to pinpoint specific SNPs or mutations that may play a role in T2DM susceptibility. The results of HRM show the melting curves that represent the dissociation of double-stranded DNA as the temperature increases. The consistent and smooth downward trend across the samples reflects a similar melting behavior, with melting transitions occurring between approximately 80.5 °C and 84.5 °C (Figure 1). The close pattern of curves in melting profiles between the different samples indicates there was no change in the sequence of this region e.g., no single nucleotide polymorphisms (SNPs) or other small genetic variations within exon 3 of the *ATG16L1* gene. The absence of major shifts or distinct outliers in the melting patterns further emphasizes that exon 3 contains no changes in its sequence that might influence its function. The lack of deviations in the melting temperature in this region was further confirmed by the sequencing technique (Figure 2). The alignment of the sequencing data was compared with the reference sequence of the *ATG16L1* gene and the analysis confirmed that the selected region appeared to have remained largely conserved in the T2DM cohort. This consistency is consistent with the overlapping patterns of the HRM melt curves, suggesting that the *ATG16L1* gene function in type 2 diabetes may be influenced by factors other than exon 3, or by more systemic genetics.

DISCUSSION

The *ATG16L1* gene plays a fundamental role in the process of autophagy, a process which is critical for maintaining cellular homeostasis. To our

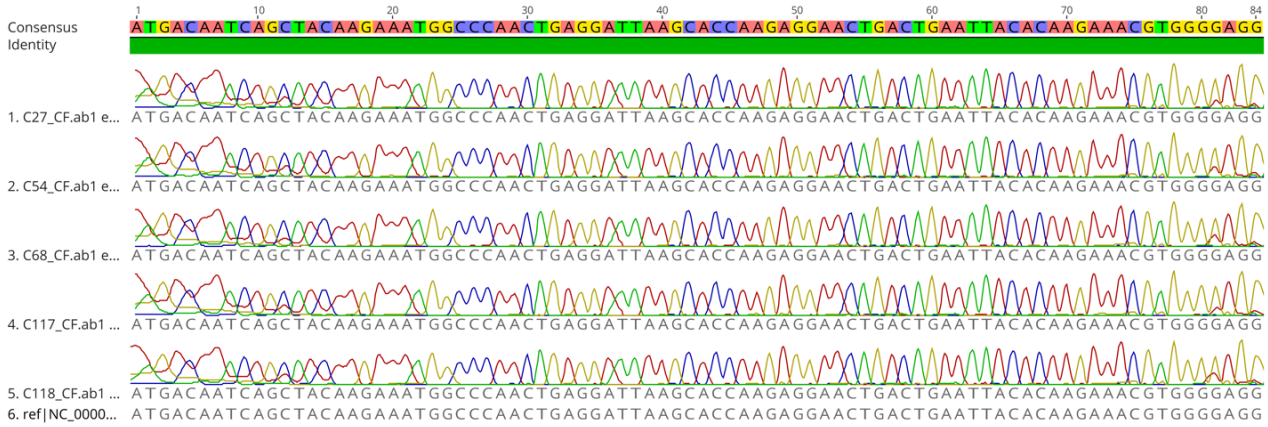

Figure 2. Sequence alignment results for exon 3 of the *ATG16L1* gene

knowledge there have been no previous studies investigating the relationship between *ATG16L1* gene polymorphisms and diabetes patients, and few studies on the relationship of *ATG16L1* gene polymorphisms and other diseases. We conducted this study to determine whether any of the expected SNPs were associated with T2DM to advance a step in the understanding of the genetic factors that increase T2DM susceptibility and to help other researchers in their investigations.

ATG16L1 represents a critical node in various physiological and pathological processes, one of which is diabetes. Due to the fact that autophagy protects cells from oxidative stress, a possible reason for hyperglycemia might be the failure of the autophagic mechanism in beta cells which exacerbates beta cells activity (6). According to Gao et al., the *ATG16L1* gene may play a significant role as a biomarker in the onset and progression of diabetic retinopathy (15). That suggests a crucial role of autophagy and, indeed, of the *ATG16L1* gene in diabetes. A previous study revealed that type 2 diabetes patients' beta cells have abnormalities in autophagy (16). We were, however, unable to identify any genetic polymorphism in our population of T2DM. This study has some limitations: the small sample size and that the region of the *ATG16L1* gene under investigation was limited to exon 3.

CONCLUSION

Our work is among the initial investigations exploring the correlation between the *ATG16L1* gene polymorphisms and T2DM. Our results indicate that the *ATG16L1* gene remains a wild sequence and contains no SNP in the exon 3 region that is linked to T2DM patients. Further studies with larger sample size on different exons of the *ATG16L1* gene are needed to determine if any SNP is associated with T2DM.

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The current study received no funding.

CONFLICT OF INTEREST

No conflicts of interest.

ADDITIONAL INFORMATION

Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020; 21(17):6275. PubMed PMID: 32872570
2. Tian Y, Xu J, Huang T, Cui J, Zhang W, Song W, et al. A novel polymorphism (rs35612982) in CDKAL1 is a risk factor of type 2 diabetes: a case-control study. Kidney Blood Press Res. 2019;44:1313-26.
3. Ghodsi M, Keshtkar AA, Razi F, Mohammad Amoli M, Nasli-Esfahani E, Zarrabi F, et al. Association of vitamin D receptor gene polymorphism with the occurrence of low bone density, osteopenia, and osteoporosis in patients with type 2 diabetes. J Diabetes Metab Disord. 2021;20:1375-83.
4. Xiong Q, Li W, Li P, Yang M, Wu C, Eichinger L. The role of ATG16 in autophagy and the ubiquitin proteasome system. Cells. 2019;8:2. PubMed PMID: 30577509
5. Saitoh T, Fujita N, Jang MH, Uematsu S, Yang B-G, Satoh T, et al. Loss of the autophagy protein Atg16L1 en-

hances endotoxin-induced IL-1β production. Nature. 2008;456(7219):264-8.
6. Watada H, Fujitani Y. Minireview: Autophagy in pancreatic β-cells and its implication in diabetes. Mol Endocrinol. 2015;29:338-48.
7. Liu H, Cao M-m, Wang Y, Li L-c, Zhu L-b, Xie G-y, et al. Endoplasmic reticulum stress is involved in the connection between inflammation and autophagy in type 2 diabetes. Gen Comp Endocrinol. 2015;210:124-9.
8. Sehrawat A, Mishra J, Mastana SS, Navik U, Bhatti GK, Reddy PH, et al. Dysregulated autophagy: A key player in the pathophysiology of type 2 diabetes and its complications. Biochim Biophys Acta Mol Basis Dis. 2023;1869(4):166666. PubMed PMID: 36791919
9. Gammoh N. The multifaceted functions of ATG16L1 in autophagy and related processes. J Cell Sci. 2020; 133(20):jcs249227. PubMed PMID: 33127840
10. Barlow AD, Thomas DC. Autophagy in diabetes: β-Cell dysfunction, insulin resistance, and complications. DNA Cell Biol. 2015;34:252-60.
11. Marasco MR, Linnemann AK. β-Cell autophagy in diabetes pathogenesis. Endocrinology. 2018;159:2127-41.
12. Alnaji HA, Omran R, Hasan AH, Al Nuwaini MQ. Diabetic retinopathy progression associated with haplotypes of two VEGFA SNPs rs2010963 and rs699947. Egyptian Journal of Basic and Applied Sciences. 2023; 10:123-34.
13. Alnaji HA, Alnaji HA, Hassan AH. Alterations of thyroid hormone levels and the risks of diabetic retinopathy in T2DM. Research Journal of Pharmacy and Technology. 2023;16:1053-9.
14. Alnaji HA, Hasan AH, Omran R, Al Nuwaini MQ. Association between the rs1800624 and rs80096349 SNPs and diabetic retinopathy: a pilot study. Ophthalmic Genet. 2025;46:40-6.
15. Gao X, Du Y, Lau WB, Li Y, Zhu S, Ma X-L. Atg16L1 as a novel biomarker and autophagy gene for diabetic retinopathy. J Diabetes Res. 2021; 2021:5398645. Pub Med PMID: 33791389
16. Masini M, Bugliani M, Lupi R, Del Guerra S, Boggi U, Filipponi F, et al. Autophagy in human type 2 diabetes pancreatic beta cells. Diabetologia. 2009;52:1083-6.

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Original Article

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Recognition of Three Common Work-Related Hand Diseases in a Teaching Hospital

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ABSTRACT

OBJECTIVE Musculoskeletal disorders (MSDs) of the hands are increasingly affecting workers in various occupations. They reduce productivity and cause economic loss. In Thailand, work-related MSDs are considered underdiagnosed and under-reported. This study aimed to determine the proportion of three major recognized hand diseases that are work-related and to examine factors associated with that recognition and work-relatedness.

METHODS This is a cross-sectional study, recruiting and interviewing patients with carpal tunnel syndrome (CTS), trigger finger (TF), and de Quervain's tenosynovitis (DQT) aged 18-65 years old who visited the Hand Clinic in the Orthopedics Department, Ramathibodi Hospital between 25 October 2023 and 15 March 2024. Patient medical records were reviewed to determine work-relatedness using NIOSH criteria. Recognition was determined by taking patient work histories. Logistic regression was used to examine the associations between work and MSDs, and between recognition and patients' factors.

RESULTS A total of 270 patients were included: 127 CTS cases, 96 TF cases, and 47 DQT cases. Almost two-thirds (63.0%) of the diseases were attributed to work-related conditions. Factors associated with work-relatedness of the three diseases were: working for 26 or more hours per week (adjusted ORs 3.26-4.63), tool use (ORadj 7.92, 95%CI [2.83, 22.17]), computer use (ORadj 4.72, 95%CI [1.84,12.14]), writing (ORadj 4.88, 95%CI [1.53, 15.61]), and having a single job (ORadj 10.13, 95%CI [2.59,39.57]). The proportion of recognition by physicians of the connection between working history and MSDs was only 13.0%. There were no significant associations between patients' personal/work factors and recognition by doctors.

CONCLUSIONS This study showed that 63.0% three common hand diseases of patients are attributed to work-related conditions, but the recognition by doctors of that relationship was only 13.0%. Factors associated with work-relatedness were mostly aspects of patients' work. The hospital should improve its system for identifying the work-related MSDs to help ensure patients receive appropriate health-related welfare and benefits. Further studies should be conducted to explore means of increasing physician recognition of work-related MSDs.

KEYWORDS work-related hand disease, carpal tunnel syndrome, trigger finger, De Quervain's tenosynovitis

INTRODUCTION

Musculoskeletal disorders (MSDs) are affecting an increasing number of workers around the world. MSDs are associated with reduced work productivity, resulting in monetary losses both for the patient and businesses. MSDs caused a median of eight sick leave days from work annually in the United States in 2020, longer than the median of five days due to other non-fatal illnesses such as digestive or respiratory problems (1). The global burden of MSDs attributable to occupational factors was 13.7% of disability-adjusted life years (DALYs) according to WHO (2). In the United States, 70 million hospital visits are contributed to by MSDs annually, as well as an estimated 130 million total healthcare encounters, including outpatient, hospital, and emergency room visits (3). The working population accounts for 79.0% of those MSDs cases, and hands are the most frequently affected organ (4, 5).

The three most common work-related hand diseases are carpal tunnel syndrome, radial styloid tenosynovitis (de Quervain's tenosynovitis), and chronic tenosynovitis of the hand and fingers (trigger finger) (6-8). Carpal tunnel syndrome results from compression or entrapment of the median nerve in its passage through the carpal tunnel. The main clinical manifestations are numbness, pain, and tingling in the thumb, index finger, middle finger, and the radial half of the ring finger of the palmar side of the affected hand (9, 10). The global incidence rate is 23 cases per 1,000 person-years (11). De Quervain's tenosynovitis is a painful condition that involves tendon entrapment affecting the first dorsal compartment of the wrist. The main symptom is pain in the anatomical snuffbox which is made worse by abduction and/or thumb extension (12, 13). In 2009 The incidence rate in persons older than 40 was 2.0 per 1,000 person-years (14). Trigger finger symptoms vary from a tender lump at the base of a finger or thumb, stiffness, and popping to a locking sensation with finger or thumb movement (13, 15). The incidence in 2021 was 0.3 per 1,000 person-years, or a lifetime risk of 2.6% in the general population (16).

These three diseases can often result from hand-using job tasks such as those involving extensive hand use (grasping/pinching) and repeated hand/arm movements (6, 17-19). These work-related MSDs (WRMSDs) have become more prominent as more people work with computers and other electronic devices (6, 20-22). These three common WRMSDs have been included on the List of Occupational Diseases by the International Labor Organization since 2010 (23) and in Thai laws since 2023 (24). Recognition of the work-relatedness by physicians is important for detecting and reporting work-related and occupational disease cases, which could help determine the extent of the disease burden. However, presently under-reporting of WRMSDs makes it difficult to determine the extent of the problem (3, 25). This study aimed to determine the proportion of physician's recognition of these three work-related hand diseases among patients age 18-65 years at Ramathibodi Hospital and to examine factors associated with these work-related cases, e.g., demographic and socio-economic status, working conditions, and job descriptions.

METHODS

Research design and setting

This cross-sectional analytical study recruited patients with one or more of three major musculoskeletal hand diseases: carpal tunnel syndrome, trigger finger, and de Quervain's tenosynovitis.

Participants

The target population was patients aged 18-65 years who visited the Hand Clinic in the Orthopedics OPD, Ramathibodi Hospital between 25 October 2023 and 15 March 2024. Patients with selected ICD-10 diagnosis code G56.0 (carpal tunnel syndrome; CTS), M65.3 (trigger finger; TF) and/or M65.4 (de Quervain's tenosynovitis; DQT) were included in this study.

Definition of work-related disease

The diseases were determined to be work-related using NIOSH's six-step approach (26, 27). The criteria included six factors: 1) evidence of disease, 2) epidemiology, 3) evidence of individual exposure, 4) consideration of other relevant factors, 5) validity of testimony, and 6) conclusions. Diseases of patients who satisfied two or more criteria were considered work-related. The work-relatedness determination of the cases included in this study was made by a doctor certified with basic occupational medicine training.

Definition of recognition of work-related conditions

A case with a work-related cause was defined as "recognized" if the doctor recorded any notes about work-related details in the patient's medical record, e.g., job titles, job descriptions, work processes, and working environment.

Data collection

Patients with MSDs of interest based on ICD-10 diagnoses who had visited the Orthopedics OPD between October 25, 2023 and March 15, 2024 were asked to complete interviews using a modified repetitive strain injury questionnaire adapted from the Strain Index and ACGIH TLV for HAL. (28, 29) The questionnaire consisted of two components: 1) personal history (smoking history and postpartum/pregnancy history), working history (job position, job description, workplace, working years, working days per week, working hours per day), and 2) details of hand motions during work (hand position, hand use time, computer use, tool use, etc.). In addition, the demographic data included age, sex, weight, height and body mass index (BMI). Evidence of exposure to repetitive hand motion before the onset of the disease was also documented. Data retrieved from electronic medical records from the Informatics Division included underlying diseases, patient health benefit schemes, and doctors' notes. The primary investigator reviewed all medical records and marked them as "recognition of work-relatedness" if the patients' records contained work-related details documented by the physician.

Outcome variables were the three MSDs (CTS, TF, DQT), WRMSDs, and the recognition of work-relatedness. Independent variables were divided into sociodemographic variables (age, sex, BMI, educational level, underlying disease), work-related variables (job group, hand use, dominant hand, working hours, workplace), and other variables (leisure activities, smoking).

Statistical analysis

The outcome variables were calculated as percentages for each of the three MSDs, WRMSDs, and the physician's recognition of work-relatedness. Differences were tested using Pearson's chi-square test with a $p < 0.05$ indicating statistical significance.

Associations between outcomes and the independent variables were tested by logistic regression using univariate and multivariate models. The odds ratios and 95% confidence intervals (CI) were used to quantify the strength of associations. The multiple logistic regression model included independent variables with a $p \leq 0.1$ in the univariate model. Data was analyzed using STATA version 17.

Ethics approval and consent

This study was approved by the Ethical Review Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (COA. No. MURA2023/771), and all participants gave written consent.

RESULTS

The total of 270 cases included 127 cases of carpal tunnel syndrome (CTS) (47.0%), 96 cases of trigger finger (TF) (36.0%), and 47 cases of de Quervain's tenosynovitis (DQT) (17.0%). Most were female (84.4%) and half the participants (52.2%) were in the age group 41-59 years. Obese patients (BMI > 24.9) were the largest group at 48.9%. In addition, 63.0% of the participants had a Civil Servant Medical Benefits Scheme (CSMBS) and 52.5% had educational levels of university graduate or above. Most received a monthly income of either less than 30,000 baht (46.3%) or between 30,000-69,999 baht (40.1%). Patient characteristics were similar among the three MSDs, with the exception of postpartum and smoking conditions. Details are shown in Table 1.

Work characteristics

Table 2 shows that skilled labor had the highest percentage of cases (46.7%), followed by educated skilled labor (33.0%). The industries with the highest number of cases were sales and manufacturing (46.7%), followed by services (33.0%). Most workers performed a single job (93.3%) and most had a break time of more than 10 minutes per day (93.3%).

Regarding the participants' hand usage, most used their hands during 50.0% or more of their work time (84.4%) and most made repetitive hand movements six or more times per minute (63.3%). The largest proportion used tools or other equipment in their jobs (37.4%), followed by computer

Table 1. Demographic characteristics of participants

Demographic characteristics	CTS n = 127 (%)	TF n = 96 (%)	DQT n = 47 (%)	Total N = 270 (%)	*p*-value
Age (year): Median (IQR) 58 (50,62), Min 20, Max 65					0.013*
20-40	15 (11.8)	5 (5.2)	7 (14.9)	27 (10.0)	
41-59	76 (59.8)	44 (45.8)	21 (44.7)	141 (52.2)	
60-65	36 (28.4)	47 (49.0)	19 (40.4)	102 (37.8)	0.544
Sex: female	110 (86.6)	78 (81.3)	40 (85.1)	228 (84.4)	
BMI: Median (IQR) 24.8 (22.1,28.8), Min 16.6, Max 41.4					
<23	40 (31.5)	32 (33.3)	15 (31.9)	87 (32.2)	0.996
23–<25	25 (19.7)	17 (17.7)	9 (19.2)	51 (18.9)	
≥25	62 (48.8)	47 (49.0)	23 (48.9)	132 (48.9)	
Health scheme					
CSMBS	88 (69.3)	54 (56.2)	28 (59.5)	170 (63.0)	0.385
SSS	10 (7.9)	14 (14.6)	7 (14.9)	31 (11.5)	
UC	11 (8.6)	9 (9.4)	6 (12.8)	26 (9.6)	
Out-of-pocket	18 (14.2)	19 (19.8)	6 (12.8)	43 (15.9)	
Educational level					
Middle and lower	48 (37.8)	26 (27.1)	12 (25.5)	86 (31.8)	0.371
High school	21 (16.5)	16 (16.7)	8 (17.0)	45 (16.7)	
Higher education	58 (45.7)	54 (56.2)	27 (57.5)	139 (51.5)	
Income level (month)					
<30,000	55 (43.3)	50 (52.1)	20 (42.5)	125 (46.3)	0.459
30,000–69,999	62 (48.8)	36 (37.5)	21 (44.7)	119 (40.1)	
≥70,000	10 (7.8)	10 (10.4)	6 (12.7)	26 (9.6)	
Underlying conditions					
DM	17 (13.4)	18 (18.7)	10 (21.3)	45 (16.7)	0.367
Hypothyroidism	4 (3.2)	2 (2.1)	2 (4.3)	8 (3.0)	0.761
Post-partum	0 (0.0)	0 (0.0)	3 (6.4)	3 (1.1)	0.001
Smoking	0 (0.0)	0 (0.0)	4 (8.5)	4 (1.5)	0.000

*$p < 0.05$

IQR, interquartile range; BMI, body mass index; CSMBS, Civil Servant Medical Benefit Scheme; SSS, Social Security Scheme, UC, Universal Coverage; DM, diabetes mellitus; CTS, carpal tunnel syndrome; TF, trigger finger; DQT, de Quervain's tenosynovitis

use (27.8%). Computer-using participants used their hands mostly for mouse clicking/scrolling more than 6 times per minute or keyboard typing more than 18 times per minute. The patient's illness mainly affected the dominant hand (94.4%), but only 41.1% had limited use of that hand. A total of 63.3% of the cases were determined to be work-related. There were no significant differences in work-relatedness among the three MSDs.

Work-related musculoskeletal diseases

Of the 171 cases that were determined to be work-related, 81 cases (63.8%) had CTS, 65 (67.7%) had TF, and 25 (53.2%) had DQT. Statistically significant factors identified by univariate analysis were female sex, having no related underlying diseases (DM, hypothyroidism), work time per week of more than 20 hours, hand-using other than general use, repetitively doing a single job, and repeated hand-use related to a hobby. Smoking and postpartum factors were not included because the limited number of participants led to not applicable (N/A) results. When the statistically significant variables were tested for collinearity, hand-use in a hobby was found to be correlated with that single job; therefore, it was removed from the multivariate model. The multivariate model found significant associations in patients without related underlying diseases (DM, hypothyroidism), work time per week of 26 hours and above, hand-using other than general use, and doing a single job.

Patients with longer work hours per week had higher adjusted odds of a work-related cause: 3.26 (1.35,7.89) in the '26-29 hours per week' group and 4.48 (1.65,12.18) in the '30 or more hours per week' group. Additionally, tool-using had higher adjusted odds compared to computer use and writing, 7.92 (2.83,22.17), 4.72 (1.84,12.14), and 4.88 (1.53,15.61), respectively. Details are shown in Table 3.

Table 2. Work-related characteristics of participants

Working characteristics	CTS n = 127 (%)	TF n = 96 (%)	DQT n = 47 (%)	Total N = 270 (%)	*p*-value
Job group (ISCO-08)					
Educated skilled labor	43 (33.9)	29 (30.2)	17 (36.2)	89 (33.0)	0.752
Skilled labor	62 (48.8)	44 (45.8)	20 (42.5)	126 (46.7)	
General labor	22 (17.3)	23 (24.0)	10 (21.3)	55 (20.3)	
Workplace (TSIC)					
Services	40 (31.5)	29 (30.2)	17 (36.2)	89 (33.0)	0.752
Sales & manufacturing	36 (28.3)	44 (45.8)	20 (42.5)	126 (46.7)	
Supportive organization	51 (40.2)	23 (24.0)	10 (21.3)	55 (20.3)	
Hand-using					
Tool-use	41 (32.3)	45 (46.9)	15 (31.9)	101 (37.4)	0.342
Computer-use	37 (29.1)	23 (24.0)	15 (31.9)	75 (27.8)	
Writing	23 (18.1)	11 (11.4)	6 (12.8)	40 (12.8)	
General use	26 (20.5)	17 (17.7)	11 (23.4)	54 (20.0)	
Hand-using work time					
≥50.0%	108 (85.0)	82 (85.4)	38 (80.8)	228 (84.4)	0.754
<50.0%	19 (15.0)	14 (14.6)	9 (19.2)	42 (15.6)	
Computer-using					
≥50.0%	48 (37.8)	28 (29.1)	16 (34.0)	92 (34.1)	0.765
<50.0%	27 (21.3)	23 (24.0)	11 (23.4)	61 (22.6)	
None	52 (40.9)	45 (46.9)	20 (42.5)	117 (43.3)	
Mouse click/scroll					
≥6/min	48 (37.8)	28 (29.1)	16 (34.0)	92 (34.1)	0.765
<6/min	27 (21.3)	23 (24.0)	11 (23.4)	61 (22.6)	
None	52 (40.9)	45 (46.9)	20 (42.5)	117 (43.3)	
Keyboard-typing					
≥18/min	48 (37.8)	28 (29.1)	16 (34.0)	92 (34.1)	0.765
<18/min	27 (21.3)	23 (24.0)	11 (23.4)	61 (22.6)	
None	52 (40.9)	45 (46.9)	20 (42.5)	117 (43.3)	
Hand movement					
≥6/min	77 (60.6)	62 (64.6)	32 (68.1)	171 (63.3)	0.631
<6/min	50 (39.4)	34 (35.4)	15 (31.9)	99 (36.7)	
Break time	119 (93.7)	88 (91.7)	46 (97.9)	253 (93.7)	0.357
Hand vibration	4 (3.2)	3 (3.1)	2 (4.3)	9 (3.3)	0.928
Single job	117 (92.1)	92 (95.8)	43 (91.5)	252 (93.3)	0.468
Hand use in hobby	19 (15.0)	14 (14.6)	9 (19.2)	42 (15.6)	0.754
Affected hand					
Dominant	124 (97.6)	88 (91.7)	43 (91.5)	255 (94.4)	0.097
Non-dominant	3 (2.4)	8 (8.3)	4 (.5)	15 (5.6)	
Current symptom					
Pain/numbness	44 (34.6)	31 (32.3)	20 (42.5)	95 (35.2)	0.475
Symptom-free	83 (65.4)	65 (67.7)	27 (57.5)	175 (64.8)	
Current hand use					
Normal	74 (58.3)	58 (60.4)	27 (57.5)	159 (58.9)	0.926
Limited	53 (41.3)	38 (39.6)	20 (42.5)	111 (41.1)	
Work-relatedness	81 (63.8)	65 (67.7)	25 (53.2)	171 (63.3)	0.236

ISCO-08, International Standard Classification of Occupations 2008; TSIC, Thailand Standard Industrial Classification; CTS, carpal tunnel syndrome; DQT, de Quervain's tenosynovitis; TF, trigger finger

Recognition of work-related conditions

Overall, 31 of the cases (13.0%) were recognized by medical professionals as work-related conditions: 19 cases (15.0%) of CTS, two cases (2.1%) of TF, and 10 cases (21.3%) of DQT. Patients with TF tended to be unrecognized 12.7 times more frequently than patients with DQT (95%CI = 2.65, 60.75). In the univariate analysis, only Health Scheme CSMBS showed some association with the recognition of work-relatedness. However,

Table 3. Association between factors and work-related cases

Factor	Work-related outcome		Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
	Yes n = 171 (%)	No n = 99 (%)		
Sex				
Female	150 (65.8)	78 (34.2)	1.92* (0.99,3.73)	1
Male	21 (50.0)	21 (50.0)	1	1.07 (0.42,2.68)
Age group				
20–40	19 (70.4)	8 (29.6)	1.80 (0.72,4.49)	1
41–59	94 (66.7)	47 (33.3)	1.51 (0.89,2.56)	1.63 (0.51,5.10)
60–65	58 (56.9)	44 (43.1)	1	1.06 (0.33,3.35)
BMI				
<23	27 (31.0)	60 (69.0)	1.49 (0.84, 2.64)	1.35 (0.64,2.86)
23–< 25	19 (37.3)	32 (62.7)	1.13 (0.58, 2.20)	1.22 (0.51,2.96)
≥25	53 (40.2)	79 (59.8)	1	1
Non-DM	152 (67.6)	73 (32.4)	2.83* (1.47,5.44)	2.35** (1.19,6.75)
Non-hypothyroidism	170 (64.9)	92 (35.1)	12.93* (1.56,106.75)	13.97** (1.34,146.13)
Affected hand			1.16 (0.40,3.36)	-
Dominant	162 (63.5)	93 (36.5)	1	-
Non-dominant	9 (60.0)	6 (40.0)	1	1
Health Scheme				
CSMBS	100 (58.8)	70 (41.2)	2.01 (0.85,4.75)	2.03 (0.65,6.39)
SSS	23 (74.2)	8 (25.8)	1.32 (0.55,3.13)	1.00 (0.28,3.56)
UC	17 (65.4)	9 (34.6)	1.80 (0.86,3.76)	1.06 (0.42,2.70)
Out-of-pocket	31 (72.1)	12 (27.9)		
Job groups				
Educational skilled labor	54 (60.7)	35 (39.3)	1.11 (0.55,2.19)	1.40 (0.47,4.18)
Skilled labor	85 (67.5)	41 (32.5)	1.49 (0.77,2.86)	1.92 (0.73,5.06)
General labor	32 (58.2)	23 (41.8)	1	1
Worktime/week				
≤20 hours	41 (38.7)	65 (61.3)	1	1
21-25 hours	31 (73.8)	11 (26.2)	4.46* (2.02,9.85)	2.11 (0.81,5.51)
26-29 hours	45 (75.0)	15 (25.0)	4.75* (2.35,9.60)	3.26** (1.35,7.89)
≥30 hours	54 (87.1)	8 (12.9)	10.70* (4.62,24.76)	4.48** (1.65,12.18)
Hand using				
Tool-use	79 (78.2)	22 (21.8)	14.03* (6.22, 31.6)	7.92** (2.83,22.17)
Computer-use	51 (68.0)	24 (32.0)	8.30* (3.65, 18.9)	4.72** (1.84,12.14)
Writing	30 (75.0)	10 (25.0)	11.73*(4.42, 31.1)	4.88** (1.53,15.61)
General use	11 (20.4)	43 (79.6)	1	1
Single job	167 (66.3)	85 (33.7)	6.87*(2.19,21.53)	10.13** (2.59,39.57)
Break time	163 (64.4)	90 (35.6)	2.03 (0.75,5.46)	-
Hand-use in hobby	10 (23.8)	32 (76.2)	2.21* (1.32,3.69)	-

*$p < 0.1$; **$p < 0.05$

DM, diabetes mellitus; BMI, body mass index; CSMBS, Civil Servant Medical Benefit Scheme; SSS, Social Security Scheme, UC, Universal Coverage

in the multivariate model, there were no statistically significant associations. Smoking and postpartum were not included because the number of patients was too small to analyze. Details are shown in Table 4.

DISCUSSION

This study found that among patients with the three most common hand MSDs, 63.3% of the cases were determined to be associated with work-related conditions based on NIOSH criteria. In contrast, only 13.0% were recognized based on their work history. Work factors such as the type of hand use, hand use in hobbies, work hours, and having a single job were statistically significantly associated with work-related conditions. No factors were significantly related to the non-recognition of work-relatedness, which could have resulted

Table 4. Association between factors and unrecognized cases of work-related hand diseases

Factor	Recognition of work-relatedness		Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
	Recognized n = 31 (%)	Not recognized n = 239 (%)		
Sex: male	3 (7.1)	39 (92.9)	1.82 (0.53,6.28)	2.02 (0.55,7.41)
Age group				
20-40	5 (18.5)	22 (81.5)	1	1
41-59	18 (12.8)	123 (87.2)	1.53 (0.52,4.61)	1.55 (0.47,5.11)
60-65	8 (7.8)	94 (92.2)	2.67 (0.79,8.95)	2.59 (0.70,9.59)
BMI				
<23	10 (11.5)	77 (88.5)	1.23 (0.43, 3.44)	1.09 (0.36,3.32)
23–<25	7 (13.7)	44 (86.3)	1	1
≥25	14 (10.6)	118 (89.4)	1.34 (0.51,3.54)	1.32 (0.48,3.65)
Health Scheme				
CSMBS	17 (10.0)	153 (90.0)	2.63* (0.99,6.99)	2.72 (0.89,2.83)
SSS	7 (22.6)	24 (77.4)	1	1
UC	3 (11.5)	23 (88.5)	2.24 (0.51,9.71)	2.47 (0.48,12.73)
Out-of-pocket	4 (9.3)	39 (90.7)	1.84 (0.75,10.74)	3.48 (0.77, 14.72)
Education level				
Middle school	12 (14.0)	74 (86.0)	1.13 (0.41,3.12)	1.06 (0.35,3.16)
High school	7 (15.6)	38 (84.4)	1	1
Higher education	12 (8.6)	127 (91.4)	1.95 (0.71,5.30)	1.59 (0.65,3.88)
Workplace				
Services	9 (11.3)	71 (88.8)	1.06 (0.43,2.61)	1.59 (0.57,4.43)
Merchandise	9 (11.3)	71 (88.8)	1.06 (0.43,2.61)	1.14 (0.43,2.98)
Authorities	13 (11.8)	97 (88.2)	1	1

*$p < 0.1$;

BMI, body mass index; CSMBS, Civil Servant Medical Benefit Scheme; SSS, Social Security Scheme, UC, Universal Coverage

from the high percentages of non-recognition across all patients.

More than half the patients were in the age group 41-59 years old. This result aligns with the NIOSH worker health chartbook (1), which reported that 31.1% of study participants with MSDs were in the 45-59 age group. This finding also corresponds with a Canadian study where half of the participants with work-related repetitive strain injuries were between 25 and 54 years old (30). Studies from France similarly concluded that greater age was the main personal risk factor for work-related musculoskeletal disorders (WRMSDs) (22, 31).

Work hours per week was associated with WRMSDs and the incidence increased as patients worked longer hours. This result is supported by a previous study which found a similar pattern of overtime or long working hours being associated with MSDs as well as an established dose-response relationship between work duration and hand symptoms (32). Other studies have similarly found that various occupations involving both tool and computer use could be associated with WRMSDs, including forceful hand movements (20, 33-35). Repetitive movement has also been found to be associated with WRMSDs in other studies (7, 30). In this study, hand-use in hobbies was correlated with workers with a single job in the test for collinearity; therefore, it was removed from the final model. In addition, patients with a single job were statistically significantly associated with WRMSDs. This finding aligns with a recent systematic review reporting that a specific job task can lead to occupational overuse syndrome (36).

The present study found that patients with no other relevant medical conditions, i.e. diabetes mellitus, or hypothyroidism, were associated with work-related factors. In contrast, previous studies have found that diabetes mellitus and metabolic syndrome were significantly associated with MSDs (37). The present study could not interpret the results of smoking, the main factor found to be related to upper extremities MSDs in other

studies (38). We hypothesize that this is due to the limited number of participants in the present study.

MSDs of the hand were under-recognized as work-related in this study, with only 13.0% being recognized by medical professionals. This finding is similar to Yagev's study in 2008 (39) and a study in Spain in 2019 (40). Patients' personal characteristics can affect doctors' recognition of work-relatedness and can also result in a longer period to detect work-relatedness (40, 41). The present study did not find a significant difference in recognition between age groups, but, according to Ramada's 2014 study, older patients have a lower prevalence of being recognized (42). Patients paying for medical treatment out-of-pocket had the highest odds of non-recognition, but the association was not statistically significant. That might be due to patients with this health care scheme being generally older and mostly retired. There is only limited evidence regarding the relationship between health benefit schemes and recognition of work-relatedness.

The results of this study demonstrate the low recognition of WRMSDs, which could result in patients not receiving appropriate authorized welfare and other health-care benefits. This study could not identify factors related to under-recognition; however, factors associated with work-relatedness were identified and could be used in developing screening questions to increase recognition, e.g., the type of hand use and work hours. Furthermore, another study showed that establishing a special occupational medicine unit could also help improve recognition (40).

The present study is among the first in Thailand to explore factors associated with MSDs of the hand without regard to the participant's occupation in a health care setting. All eligible subjects were enrolled, and the response rate was 100.0%. Limitations of this study include the small sample size which, due to time limitations, was less than originally planned. Participants may also have had recall bias. Finally, the study only examined patient factors, omitting the potential influence of physicians' experience and knowledge. Orthopedists see a substantial number of patients with WRMSDs; therefore, their insights could benefit efforts to increase the recognition of WRMSDs in the future.

CONCLUSION

This study examined the three major work-related hand diseases, CTS, TF and DQT, in working patients at Ramathibodi Hospital in 2022-2023. The prevalence of work-related cases was 63.0%, but the recognition of that relatedness by attending physicians was only 13.0%. Factors associated with work-relatedness were working longer hours, working with tools, using computers, writing, having a single job, and no underlying DM or hypothyroidism. Hospitals should develop screening systems to identify patients with work-related diseases and should also seek ways to assist patients to receive authorized welfare and other benefits. Further studies should also be conducted to explore ways to increase recognition by physicians or connections between a patient's working situation and MSDs.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion. Work-Related Musculoskeletal Disorders & Ergonomics. CDC A [Internet]. 2020 [cited Feb 12, 2020]. Available from: https://www.cdc.gov/workplacehealthpromotion/health-strategies/musculoskeletal-disorders/index.html
2. Nogueira C, Kocks D, Frost C. WHO/ILO Joint Estimates of Work-related Burden of Disease and Injury. Occup Health South Afr. 2021;27:179-80.
3. Boden L. Capture-recapture estimates of the undercount of workplace injuries and illnesses: sensitivity analysis. Am J Ind Med. 2014;57:1090-9.
4. Briggs A, Cross M, Hoy D, Sànchez-Riera L, Blyth F, Woolf A, et al. Musculoskeletal Health Conditions Represent a Global Threat to Healthy Aging: A Report for the 2015 World Health Organization World Report on Ageing and Health. The Gerontologist.

2016;56(Supplement_2):S243-55.
5. Briggs A, Woolf A, Dreinhöfer K, Homb N, Hoy D, Kopansky-Giles D, et al. Reducing the global burden of musculoskeletal conditions. Bull World Health Organ. 2018;96:366-8.
6. Hulshof CTJ, Pega F, Neupane S, van der Molen HF, Colosio C, Daams JG, et al. The prevalence of occupational exposure to ergonomic risk factors: A systematic review and meta-analysis from the WHO/ILO joint estimates of the work-related burden of disease and injury. Environ Int. 2021;146:106157. PubMed PMID: 33395953
7. Iqbal Z, Alghadir A. Cumulative trauma disorders: A review. J Back Musculoskelet Rehabil. 2017;30:663-6.
8. Currie K, Tadisina K, Mackinnon S. Common Hand Conditions: A Review. Jama. 2022;327:2434-45.
9. Osiak K, Elnazir P, Walocha J, Pasternak A. Carpal tunnel syndrome: state-of-the-art review. Folia Morphol (Warsz). 2022;81:851-62.
10. Sucher B, Schreiber A. Carpal Tunnel Syndrome Diagnosis. Physical Medicine and Rehabilitation Clinics of North America. 2014;25:229-47.
11. Dale A, Harris-Adamson C, Rempel D, Gerr F, Hegmann K, Silverstein B, et al. Prevalence and incidence of carpal tunnel syndrome in US working populations: pooled analysis of six prospective studies. Scand J Work Environ Health. 2013;39:495-505.
12. Allbrook V. 'The side of my wrist hurts': De Quervain's tenosynovitis. Aust J Gen Pract. 2019;48:753-6.
13. Laoopugsin N, Laoopugsin S. The study of work behaviours and risks for occupational overuse syndrome. Hand Surg. 2012;17:205-12.
14. Wolf JM, Sturdivant RX, Owens BD. Incidence of de Quervain's tenosynovitis in a young, active population. J Hand Surg Am. 2009;34:112-5.
15. Jordaan PW, Klumpp R, Zeppieri M. Triggering, clicking, locking and crepitus of the finger: a comprehensive overview. World J Orthop. 2023;14:733-40.
16. Langer D, Maeir A, Michailevich M, Luria S. Evaluating hand function in clients with trigger finger. Occup Ther Int. 2017;2017:9539206. PubMed PMID: 29097982.
17. Balogh I, Arvidsson I, Björk J, Hansson G, Ohlsson K, Skerfving S, et al. Work-related neck and upper limb disorders - quantitative exposure-response relationships adjusted for personal characteristics and psychosocial conditions. BMC Musculoskelet Disord. 2019;20:139. PubMed PMID: 30935374.
18. Feng B, Chen K, Zhu X, Ip WY, Andersen LL, Page P, et al. Prevalence and risk factors of self-reported wrist and hand symptoms and clinically confirmed carpal tunnel syndrome among office workers in China: a cross-sectional study. BMC Public Health. 2021;21:57. PubMed PMID: 33407293.
19. Gerr F, Monteilh C, Marcus M. Keyboard use and musculoskeletal outcomes among computer users. J Occup Rehabil. 2006;16:265-77.
20. Greiner B, Nolan S, Hogan D. Work-related upper limb symptoms in hand-intensive health care occupations: a cross-sectional study with a health and safety perspective. Phys Ther. 2019;99:62-73.
21. Özdemir G. Working hand syndrome: a new definition of non-classified polyneuropathy condition. Medicine (Baltimore). 2017;96:e7235. PubMed PMID: 28640120
22. Roquelaure Y, Ha C, Rouillon C, Fouquet N, Leclerc A, Descatha A, et al. Risk factors for upper-extremity musculoskeletal disorders in the working population. Arthritis Rheum. 2009;61:1425-34.
23. International Labour Organization. List of Occupational Diseases (Revised 2010). Occupational Safety and Health Series, No. 74 [Internet]. 2010. Available from: https://www.ilo.org/publications/ilo-list-occupational-diseases-revised-2010
24. Notification of the Ministry of Labour: List of Occupational Diseases [Internet]. 2023 Available from: https://dl.parliament.go.th/handle/20.500.13072/608686 [in Thai].
25. Kreshpaj B, Bodin T, Wegman D, Matilla-Santander N, Burstrom B, Kjellberg K, et al. Under-reporting of non-fatal occupational injuries among precarious and non-precarious workers in Sweden. Occup Environ Med. 2022;79:3-9.
26. Greaves W, Das R, McKenzie J, Sinclair D 2nd, Hegmann K. Work-Relatedness. J Occup Environ Med. 2018;60:e640-6.
27. Kusnetz S HMe. A Guide to the Work-relatedness of Disease. DHEW Publication. 1979.
28. Ijmker S, Huysmans M, van der Beek A, Knol D, van Mechelen W, Bongers P, et al. Software-recorded and self-reported duration of computer use in relation to the onset of severe arm-wrist-hand pain and neck-shoulder pain. Occup Environ Med. 2011;68:502-9.
29. Kapellusch J, Garg A, Hegmann K, Thiese M, Malloy E. The Strain Index and ACGIH TLV for HAL: risk of trigger digit in the WISTAH prospective cohort. Hum Factors. 2014;56:98-111.
30. Breslin F, Ibrahim S, Smith P, Mustard C, Amick B, Shankardass K. The demographic and contextual correlates of work-related repetitive strain injuries among Canadian men and women. Am J Ind Med. 2013;56:1180-9.
31. Petit Le Manac'h A, Roquelaure Y, Ha C, Bodin J, Meyer G, Bigot F, et al. Risk factors for de Quervain's disease in a French working population. Scand J Work Environ Health. 2011;37:394-401.
32. S IJ, Huysmans MA, Blatter BM, van der Beek AJ, van Mechelen W, Bongers PM. Should office workers spend fewer hours at their computers? A systematic review of the literature. Occup Environ Med. 2007;64:211-22.
33. Betzl J, Kraneburg U, Megerle K. Overuse syndrome of the hand and wrist in musicians: a systematic review. J Hand Surg Eur Vol. 2020;45:636-42.
34. Dahlgren G, Liv P, Öhberg F, Slunga Järvholm L, Forsman M, Rehn B. Correlations between ratings and technical measurements in hand-intensive work. Bioengineering (Basel). 2023;10(7):867. PubMed PMID: 37508893

35. Huysmans M, Ijmker S, Blatter B, Knol D, van Mechelen W, Bongers P, et al. The relative contribution of work exposure, leisure time exposure, and individual characteristics in the onset of arm-wrist-hand and neck-shoulder symptoms among office workers. Int Arch Occup Environ Health. 2012;85:651-66.
36. Demissie B, Bayih E, Demmelash A. A systematic review of work-related musculoskeletal disorders and risk factors among computer users. Heliyon. 2024;10:e25075. PubMed PMID: 38318034
37. N JHS, L A, R GVG, da Silveira D, B PN, Almeida SF. Epidemiology of trigger finger: metabolic syndrome as a new perspective of associated disease. Hand (N Y). 2021;16:542-5.
38. van den Berge M, van der Beek AJ, Türkeli R, van Kalken M, Hulsegge G. Work-related physical and psychosocial risk factors cluster with obesity, smoking and physical inactivity. Int Arch Occup Environ Health. 2021;94:741-50.
39. Yagev Y, Gringolds M, Karakis I, Carel R. Carpal Tunnel Syndrome: Under-recognition of Occupational Risk Factors by Clinicians. Industrial health. 2008;45:820-2.
40. Benavides FG, Ramada JM, Ubalde-López M, Delclos GL, Serra C. A hospital occupational diseases unit: an experience to increase the recognition of occupational disease. Med Lav. 2019;110:278-84.
41. Pelegrí A, Serra C, Ramada JM, Palma-Vásquez C, Benavides FG. Waiting time from identification to recognition an occupational disease in Spain. Gac Sanit. 2022;36:257-9.
42. Ramada Rodilla JM, Delclós Clanchet J, Benavides FG, Fontané Ventura J, Arango Toro O, Serra Pujadas C. [Identification of occupational diseases in a tertiary care hospital]. Arch Prev Riesgos Labor. 2014;17:18-25.

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Comparison of Ultrasonographic and Electrodiagnostic Findings Between Healthy and CTS Thais

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ABSTRACT

OBJECTIVE To compare the ultrasonography cross-sectional area (CSA) of the median nerve at the wrist (CSA-D), the wrist-to-forearm median nerve CSA ratio (WFR) and the difference (WFD) between individuals with carpal tunnel syndrome (CTS) and normal individuals in the Thai population and to explore the correlation between ultrasonography and electrodiagnosis (EDX).

METHODS A cross-sectional study was performed on a total of 112 wrists of 72 participants who were divided into two groups. Fifty-six wrists of 36 EDX-confirmed CTS patients were recruited as the CTS group and an equal number of individuals without CTS were chosen as a control group. Participants were matched for demographic data from a historical study. For both individuals with clinical CTS confirmed by EDX and the control population median nerve CSA levels at the wrist and at mid-forearm were measured by ultrasonography. A comparison was made between the parameters of the study group and those of the control group. The correlations between the CSA-D, the WFR, and the WFD and the severity of CTS evaluated by EDX were studied.

RESULTS The mean median nerve CSA-D, WFR, and WFD of the CTS patients were 14.7 ± 5.9 mm², 3.1 ± 1.4, and 9.7 ± 6.1 mm², respectively. In contrast, the mean median nerve CSA-D, WFR, and WFD of the control group were 9.6 ± 2.4 mm², 1.7 ± 0.4, and 3.8 ± 1.9 mm², respectively, indicating a statistically significant difference from the study group ($p < 0.001$). The optimal cut-point values for the median nerve CSA-D, WFR, and WFD in detecting CTS were 10.7 mm² (sensitivity 67.9%, specificity 83.9%), 1.8 (sensitivity 89.3%, specificity 71.4%), and 4.7 mm² (sensitivity 82.1%, specificity 81.8%), respectively. The median nerve CSA-D, WFR, and WFD exhibited significant moderate to strong positive correlation with the EDX grading of CTS severity.

CONCLUSIONS Ultrasonography of the median nerve CSA-D, WFR, and WFD are efficient for distinguishing CTS patients from asymptomatic controls with good sensitivity and specificity in the Thai population. WFD demonstrated superiority in the areas of sensitivity, specificity, and accuracy.

KEYWORDS carpal tunnel syndrome, median neuropathy, ultrasonography, electrodiagnosis

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. The prevalence ranges from 3.1 to 4.6 percent in the general population (1, 2). Diagnosis often relies on clinical signs, symptoms, and physical examination. Electrodiagnosis (EDX) helps in both confirming and differentiating diagnoses, e.g., cervical radiculopathy and peripheral polyneuropathy. Additionally, it can assist in the assessment of the disease severity, which consequently informs the management planning. Treatments include conservative treatment for mild to moderate degree cases and surgical procedures for severe cases. The sensitivity and specificity of the EDX for CTS are 82.0-94.0% and 65.0-97.0%, respectively, in patients with clinical symptoms. The validity relies on neurophysiological grading, various methodological issues, including variable reference standards, measurement methods, and spectrum bias in case-control studies (2, 3). Nevertheless, there are common limitations of EDX including tissue edema, patient intolerance of the evaluation procedure, and unavailability of evaluation equipment.

Currently, high-resolution ultrasound (US) serves as an effective instrument for assessing nerve anatomy and adjacent tissues. Advantages include time-saving, simplicity, and affordability. In comparison to the clinical diagnostic reference standard, the overall sensitivity of US was 86.4% and that of EDX was 91.6%. The pooled specificities for US and EDX were 79.3% and 81.9%, respectively. There were no statistically significant differences between US and EDX in terms of sensitivity, specificity, or diagnostic accuracy. In general, US and EDX have equal diagnostic accuracy for CTS diagnosis, with both having high sensitivity and intermediate specificity (4). In CTS, nerve compression can lead to a regional circulatory disruption, causing a breakdown of the blood-nerve barrier, which increases endoneurial fluid pressure, resulting in nerve swelling and further compromising local blood flow. The median nerve is frequently swollen in the proximal part of an entrapment site as a pathophysiology of CTS; hence, the nerve's cross-sectional area (CSA) is the most typical metric for diagnosis (2). The cut-point value for median nerve CSA at the distal wrist crease (CSA-D) for diagnosing CTS has previously been reported as ≥ 8.5-12 mm² (5-9). Previous researches have indicated that ethnicity, age, height, and body mass index (BMI) affect the nerve CSA. The median nerve CSA in Europeans appears to be larger than in Asians, however, there is variation in nerve CSA within the Asian population. For that reason, utilizing the same cut-point for diagnosing CTS across different nationalities may result in the nerve CSA being beyond the precise conditions range (10-12). Thus, the ratio of the median nerve CSA-D to that at the forearm (WFR) or their difference (WFD) will mitigate the influence of these factors. Several studies have reported that the diagnostic cut-point values for the WFR and the WFD in CTS are 1.4-2.4 (5, 6, 13) and 2.5-6 mm² (5, 7), respectively, indicating good sensitivity and specificity. However, in a study of the normal Thai population, the WFR of the median nerve ranged from 1.0 to 2.3, while the median nerve CSA-D measured between 5.3 and 13.3 mm² which falls within the range of the disease group (12). Measurement of only the median nerve CSA at the wrist might result in a false positive. Integrating additional US parameters may enhance the accuracy of distinguishing CTS from normal conditions. Furthermore, the measurement locations for median nerve CSA in the forearm, that is, at the pronator quadratus (PQ) (7, 8) and 10-12 cm from the wrist (5, 14), varied across the studies. The depth of tissue in the forearm in relation to the point of measurement may influence the clarity of the nerve CSA as well. According to Junck et al., the mid-forearm location significantly outperformed the distal one-third of the forearm in terms of inter-rater reliability (r = 0.81) (15).

Some previous studies have utilized variable criteria and grading severity. Previous research of the relationship between the median nerve CSA and the severity grading from electrodiagnostic findings has yielded varied outcomes (7, 13, 14, 16). However, some of those studies did not use EDX to exclude cervical radiculopathy or polyneuropathy, which may also affect the nerve CSA (17).

The main objective of the present study is to compare the CSA-D of the median nerve, the WFR, and the WFD between individuals with CTS and healthy controls. The study also determined the cut-point values of the CSA-D, the WFR, and the WFD in detecting CTS and examined the correlation between these findings and disease severity classified by EDX in a Thai population.

METHODS

Study design

This cross-sectional research study with a historical control was approved by the Ethics Committee at Lerdsin Hospital, Bang Rak District, Bangkok. The certification number is LH661070. The number for Thai Clinical Trials Registry is TCTR20231108002.

Participants

The study group, CTS patients who had undergone EDX at the Physical Medicine and Rehabilitation Department of Lerdsin Hospital between April and August 2024 were invited to participate. The inclusion criteria consisted of individuals of Thai ethnicity, aged over 18, who were diagnosed with CTS based on positive electrodiagnostic findings combined with any of the following clinical features: (1) experiencing numbness or pain of the thumb, index finger, middle finger, or ring finger which worsened with specific activities and improved with rest or hand movements, (2) having sensory disturbances in the radial three-and-a-half fingers, (3) exhibiting varying degrees of thenar muscle weakness or atrophy, and (4) having positive results of the Tinel's Test and/or Modified Phalen's Test (2). The exclusion criteria were individuals with neurological conditions such as cervical radiculopathy, brachial plexopathy, median nerve damage due to trauma, or peripheral polyneuropathy, patients who had negative findings on EDX to confirm CTS, patients who had received a CTS injection within six months prior to the examination date, patients who had undergone CTS surgery, patients who exhibited anatomical variations (Martin-Gruber anastomosis, Riché-Cannieu anastomosis) as determined by electrodiagnostic testing and patients whose median nerve exhibited bifurcation by US. All participants submitted written informed consent.

The control group data was retrieved in a retrospective study that included healthy Thai individuals who exhibited no clinical numbness nor weakness in either hand and who had undergone electrodiagnostic testing to exclude peripheral neuropathy and had received ultrasonography examinations of the median nerve at the distal wrist and mid-forearm, following the same methodology as the study group. This study was conducted from March 2022 to May 2023 (LH651011). Age, weight, and BMI were used in matching the groups to ensure that the demographic characteristics of the control aligned closely with those of the study group. The sample size was determined according to previous studies (5, 13) by using the two independent means formula. The average and standard deviation (SD) of the median nerve CSA-D, WFR, and WFD were calculated. The delta of the mean median nerve CSA-D, WFR, and WFD were 6.2, 0.25, and 6.0 respectively. An alpha of 0.05 was selected. The power effect size was 0.8. A sample size of 30 individuals in each group was selected for the study. Considering an anticipated dropout rate of 20.0%, 72 individuals were included.

EDX of CTS

The median and ulnar nerve conduction studies (NCS), including sensory nerve action potential (SNAP) and compound motor action potential (CMAP), were conducted by physiatrists using Nicolet Synergy equipment (Natus Medical Inc., San Carlos, CA, USA). Needle electromyography (EMG) was performed on the patients who had no median CMAP response and to differentiate CTS from other conditions. Normal reference values were based on American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) 2020 (18).

Median CMAP: the active electrode was placed halfway between the midpoint of the distal wrist crease and the first metacarpophalangeal joint, and the stimulation sites were at the wrist (8 cm proximal to the active electrode) and the elbow (medial to the brachial artery pulse).

Ulnar CMAP: the active electrode was placed on the hypothenar eminence, and the stimulation sites were at the wrist (8 cm proximal to the active electrode) and the olecranon fossa.

Median SNAP: the active electrode was placed on the index finger, and the stimulation site was at the wrist, 14 cm proximal to the active electrode.

Ulnar SNAP: the active electrode was placed on the little finger, and the stimulation site was at the wrist, 14 cm proximal to the active electrode.

For patients who exhibited normal median SNAP and median CMAP, confirmatory electrophysiological evidence was defined as any difference ≥ 0.4 millisecond (ms) between: 1) a 8-cm orthodromic palmar median-ulnar peak latency difference;

2) a 14-cm antidromic median-ulnar sensory peak latency difference to the ring finger; 3) a 10-cm antidromic median-radial peak latency difference to the thumb; or 4) a combined summary index ≥ 0.9 ms (3). Skin temperature during the measurements was maintained at between 32 and 34 degrees Celsius.

The severity of CTS was classified into three levels according to Werner et al. as follows: (1) mild: prolonged (relative or absolute) sensory latency with normal motor study and no evidence of axonal loss; (2) moderate: abnormal median sensory latency as noted for mild CTS, and (relative or absolute) prolongation of median motor distal latency with no evidence of axonal loss. (3) severe: any of the aforementioned NCS abnormalities with evidence of axonal loss as defined by either (a) a low-amplitude or absent SNAP (b) a low-amplitude or absent thenar CMAP (c) a needle EMG with fibrillation potentials or motor unit action potential changes (large amplitude, long-duration motor unit potentials, or excessive polyphasics). Both hands were included if the patient exhibited clinical symptoms of CTS and had a positive EDX exam.

Ultrasonography

All individuals underwent ultrasonographic examination using a multifrequency linear transducer operating at 4-18 megahertz (MHz) (Konica Minolta, SONIMAGE® HS1, Tokyo, Japan) in B mode, conducted on the same day as the electrodiagnostic study by a single physician who was blinded to the CTS severity results. The participants were seated with their palms facing up, wrists in neutral position, and fingers slightly flexed. US was used to identify the median nerve. The transducer angle was set to be perpendicular to the nerve in order to get images with the smallest CSA and to avoid anisotropy effect. The Color Doppler test assessed the vascular component. The focus and depth were adjusted according to the target location. The CSA was measured at each location using the ellipsoid function to trace inside the nerve's hyperechoic border. The median nerve CSA at each site was calculated by averaging the results from three separate tests: the distal wrist crease (at the level of the pisiform bone) and the mid-forearm, which was determined at the midpoint between the distal wrist crease and the elbow (Figure 1).

Outcome measurements

The median nerve CSA at the distal wrist and the mid-forearm were recorded. The wrist-to-forearm median nerve CSA ratio (WFR) was calculated by dividing the nerve CSA at the wrist by the nerve CSA at the mid-forearm. The wrist-to-forearm difference (WFD) was calculated by subtracting the median nerve CSA at mid-forearm from the median nerve CSA at the distal wrist.

Statistical methods

Statistical analysis was performed using the PASW Statistics version 18.0 program. (SPSS Inc., Chicago, IL, USA). Continuous data was analyzed using an independent t-test and reported as mean and SD. The results for categorical data were analyzed using the Chi-square test and Fisher's exact test and are displayed as frequencies and

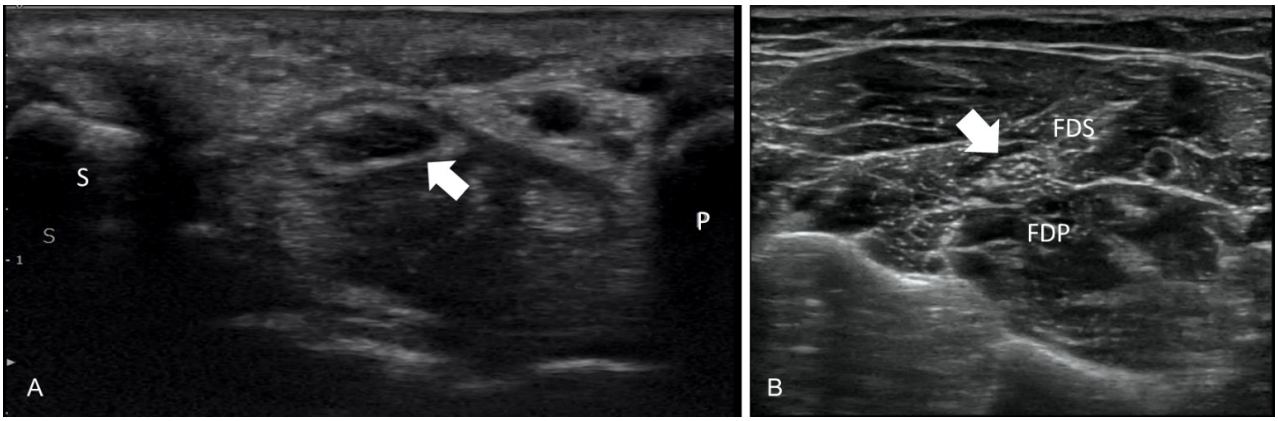

Figure 1. Ultrasonography of the nerve cross-sectional area (CSA) at each measured site. (A) median nerve at wrist, (B) median nerve at mid-forearm; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; P, pisiform bone; S, scaphoid bone. Arrows show the median nerve.

percentages. The independent t-test was employed to compare the demographic data between the study group and the control group. One-way ANOVA with Bonferroni correction was applied to compare disease severity. The receiver operating characteristic (ROC) curve was used to evaluate the cut-point value to distinguish CTS group from the control group and for differentiating severe CTS from non-severe CTS by determining the highest accuracy. Spearman correlation coefficients (r) were utilized to assess the relationship between the severity of CTS and the median nerve CSA-D, WFR, and WFD. The relationships between the median nerve CSA-D and NCS parameters were assessed using Pearson's correlation coefficient (r). A $p < 0.05$ was considered statistically significant.

RESULTS

Of 52 participants referred for CTS evaluation, 36 participants (56 wrists) were clinically diagnosed with CTS as confirmed by EDX (Figure 2). A total of 32 females were included, representing 88.9% of the sample. The mean age, weight, height, and BMI were 53.1 ± 12.4 years, 64.7 ± 17.2 kg, 157.0 ± 7.9 cm, and 26.1 ± 5.4 kg/m^2, respectively. The demographic data did not show any statistically significant differences between the study group and the control group (Table 1).

A significant difference was observed in the median nerve CSA-D, measuring 14.7 ± 5.9 mm^2 in the study group compared to 9.6 ± 2.4 mm^2 in the control group. The median nerve CSA-D (mm^2) for mild, moderate, and severe degrees was measured at 11.1 ± 2.5, 14.0 ± 4.6, and 21.4 ± 5.6, respectively, with statistically significant differences observed both between the mild to severe group and between the moderate to severe group. A notable difference in the median nerve CSA (mm^2) at the mid-forearm was seen between the study (5.0 ± 1.0) and control (5.8 ± 2.0) groups. However, there was no significant difference across the severity categories (Table 2).

The WFR of the median nerve for the study and control groups was 3.1 ± 1.4 and 1.7 ± 0.4, respectively, a statistically significant difference The groups classified as mild, moderate, and severe had mean values of 2.3 ± 0.7, 2.9 ± 1.2, and 4.6 ± 1.2, respectively. A statistically significant difference was observed between the mild and severe groups and between the moderate and severe groups (Table 2).

The WFD of the median nerve for the study group was 9.7 ± 6.1 mm^2, while for the control group it was 3.8 ± 1.9 mm^2, a statistically significant difference. The subgroups mild, moderate, and

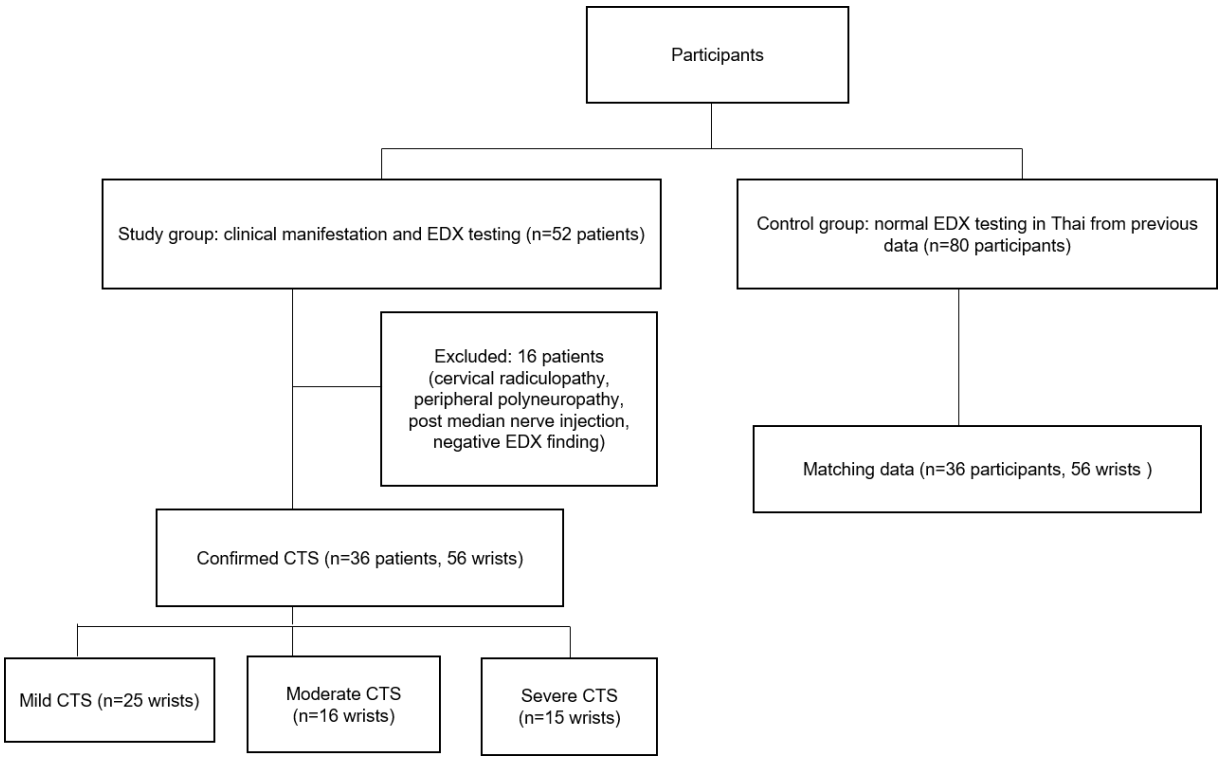

Figure 2. Flow chart of participants; EDX, electrodiagnosis; n, number; CTS, carpal tunnel syndrome

Table 1. Characteristics of patients (n = 36 individuals) with carpal tunnel syndrome and the control group (n = 36 individuals)

Parameters	CTS (n = 36) Mean (SD), (min, max)	Control (n = 36) Mean (SD), (min, max)	*p*-value
Sex[a] n (%)			
Male: female	4 (11.1):32 (88.9)	10 (27.8):26 (72.2)	0.074
Age (years)[b]			
All	53.1 (12.4), (22, 79)	52.5 (12.6), (23, 72)	0.822
Male	59.0 (11.4), (46, 73)	56.3 (8.7), (41, 72)	0.639
Female	52.4 (12.5), (22, 79)	51.0 (13.7), (23, 70)	0.684
Weight (kg)[b]			
All	64.7 (17.2), (44, 110)	61.8 (13.0), (42, 90)	0.424
Male	78.0 (16.5), (65, 101)	69.1 (11.0), (51, 85)	0.255
Female	63.1 (16.8), (44, 110)	59.0 (12.8), (42, 90)	0.318
Height (cm)[b]			
All	157.0 (7.9), (143, 174)	158.7 (7.7), (144, 175)	0.361
Male	169.0 (5.0), (163, 174)	166.4 (5.5), (158, 175)	0.432
Female	155.5 (6.9), (143, 170)	155.7 (6.3), (11, 168)	0.899
Body mass index (kg/m^2)[b]			
All	26.1 (5.4), (18.7, 38.5)	24.4 (3.9), (18.2, 34.1)	0.144
Male	27.3 (5.4), (21.5, 34.1)	24.8 (2.8), (20.4, 29.0)	0.274
Female	25.9 (5.4), (18.7, 38.5)	24.2 (4.3), (18.2, 34.1)	0.215
Underlying disease[a] n (%)			
None	33 (91.6)	36 (100.0)	
Diabetic mellitus	2 (5.6)	-	
Hypothyroidism	1 (2.8)	-	
Duration of symptoms[b] (month) median (range)	9.5 (1, 156)	-	
Severity[a] (56 wrists) n (%)			
Mild	25 (44.6)	-	
Moderate	16 (28.6)	-	
Severe	15 (26.8)	-	

[a]Chi-square test, [b]Independent t-test
CTS, carpal tunnel syndrome; SD, standard deviation; min, minimum; max, maximum; kg, kilogram; cm, centrimeter; mm^2, square millimeter

Table 2. Ultrasonographic findings of the median nerve in relation to the electrophysiological classification of carpal tunnel syndrome severity

Ultrasonographic findings	Electrophysiological classification of CTS severity (n=56 wrists): mean (SD) (min, max)				Control (n=56 wrists)	*p*-value[b]	*p*-value[a]
	All[a]	Mild	Moderate	Severe			
CSA at wrist (mm^2)	14.7 (5.9) (8.3, 32.3)	11.1 (2.5) (8.3, 20.3)	14.0 (4.6) (8.7, 24.3)	21.4 (5.6) (12.3, 32.3)	9.6 (2.4) (6.0, 17.7)	<0.001*+	<0.001#
CSA at MF (mm^2)	5.0 (1.0) (3.0, 7.7)	5.1 (1.1) (3.0, 7.7)	5.2 (0.9) (4.0, 7.0)	4.8 (0.7) (3.7, 6.0)	5.8 (2.0) (3.0, 15.7)	0.468	0.008#
WFR	3.1 (1.4) (1.4, 7.0)	2.3 (0.7) (1.4, 4.1)	2.9 (1.2) (1.6, 6.0)	4.6 (1.2) (2.6, 7.0)	1.7 (0.4) (1.1, 3.1)	<0.001*+	<0.001#
WFD (mm^2)	9.7 (6.1) (3.0, 26.3)	6.0 (2.7) (3.0, 15.3)	8.9 (4.9) (4.0, 20.0)	16.6 (5.4) (8.0, 26.3)	3.8 (1.9) (0.7, 10.7)	<0.001*+	<0.001#

[a]*p*-value compared between the study (all) and the control groups by Independent t-test, [b]*p*-value compared among the severity groups by One-Way ANOVA with Bonferroni correction, *statistical significance between mild and severe degree, +statistical significance between moderate and severe degree, #statistical significance between the study and the control groups ($p < 0.05$), CTS, carpal tunnel syndrome; SD, standard deviation; min, minimum; max, maximum; CSA, cross-sectional area; mm^2, square millimeter; MF, mid-forearm; WFR, wrist-to-forearm ratio; WFD, wrist-to-forearm difference

Table 3. Sensitivity and specificity of ultrasonographic nerve assessment in determining carpal tunnel syndrome and identifying severe carpal tunnel syndrome from non-severe patients

Ultrasonographic findings	Cut-point	Sensitivity %	Specificity %	Accuracy %
CSA at wrist (mm^2)				
CTS from control	10.7	67.9	83.9	75.9
Severe from non-severe	14.5	86.7	90.2	89.3
WFR				
CTS from control	1.8	89.3	71.4	80.4
Severe from non-severe	3.1	86.7	85.4	85.7
WFD (mm^2)				
CTS from control	4.7	82.1	81.8	82.0
Severe from non-severe	11.0	86.7	90.2	89.3

CSA, cross-sectional area; mm^2, square millimeter; CTS, carpal tunnel syndrome; WFR, wrist-to-forearm ratio; WFD, wrist-to-forearm difference

severe degrees exhibited a WFD of 6.0 ± 2.7 mm^2, 8.9 ± 4.9 mm^2, and 16.6 ± 5.4 mm^2, respectively. A statistically significant difference was found between the mild and severe groups and between the moderate and severe groups (Table 2).

In comparison of the mild and moderate CTS subgroups, no statistically significant difference was observed in the median nerve CSA-D, the CSA at the mid-forearm, the WFR, and the WFD.

ROC curves were used to determine the optimal US cut-point values to distinguish CTS group from the control group. The median nerve CSA-D, WFR, and WFD had areas under the curve (AUC) of 0.830 (95% confidence interval [CI]; 0.756, 0.905), 0.867 (95%CI; 0.801, 0.934), and 0.882 (95%CI; 0.822, 0.943), respectively. All the AUCs showed high values. The median nerve CSA-D has an optimum cut-point value of 10.7 mm^2, with a sensitivity of 67.9% and specificity of 83.9%. The WFR, with a cut-point value of 1.8, has a sensitivity of 89.3% and a specificity of 71.4%. The WFD's cut-point was determined to be 4.7 mm^2, with 82.1% sensitivity and 81.8% specificity (Table 3, Figure 3).

In differentiating severe from non-severe CTS, the AUCs for the CSA-D, WFR, and WFD in severe CTS were 0.932 (95%CI; 0.868, 0.996), 0.920 (95%CI; 0.847, 0.994), and 0.928 (95%CI; 0.861, 0.994), respectively. An optimal cut-point value for median nerve CSA-D was determined to be 14.5 mm^2, with a sensitivity of 86.7% and a specificity of 90.2%. The cut-point value of the WFR was established at 3.1, demonstrating a sensitivity of 86.7% and a specificity of 85.4%. The cut-point value of the WFD was determined to be 11.0 mm^2, with a sensitivity of 86.7% and a specificity of 90.2% (Table 3, Figure 4).

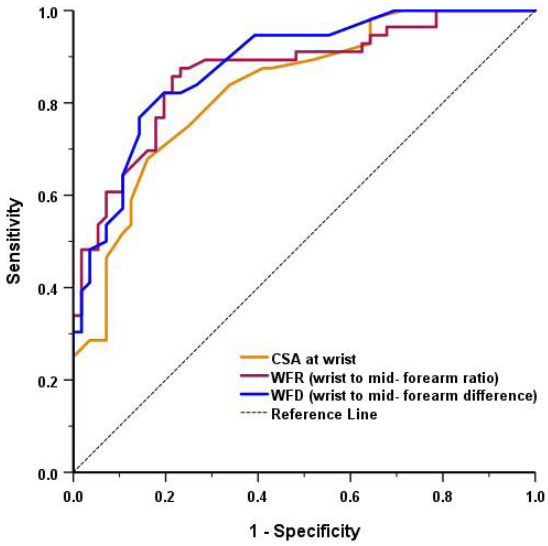

Figure 3. Receiver operating characteristic (ROC) curves with area under the curve of median nerve cross-sectional area (CSA) at the wrist, WFR (wrist-to-forearm ratio), and WFD (wrist-to-forearm difference) for diagnosing carpal tunnel syndrome

All median nerve CSA-D, WFR, and WFD values showed moderate to strong, positive and statistically significant correlation with disease severity (Table 4). A statistically significant moderate positive correlation was observed between the median nerve CSA-D and both the median SNAP latency and the median CMAP latency. The median nerve CSA-D showed a notable weak negative correlation with the amplitude of median SNAP and a moderate negative correlation with the amplitude of median CMAP. Additionally, there was a weak negative correlation with the median nerve conduction velocity (NCV) measured from the forearm to the wrist segment (Table 5).

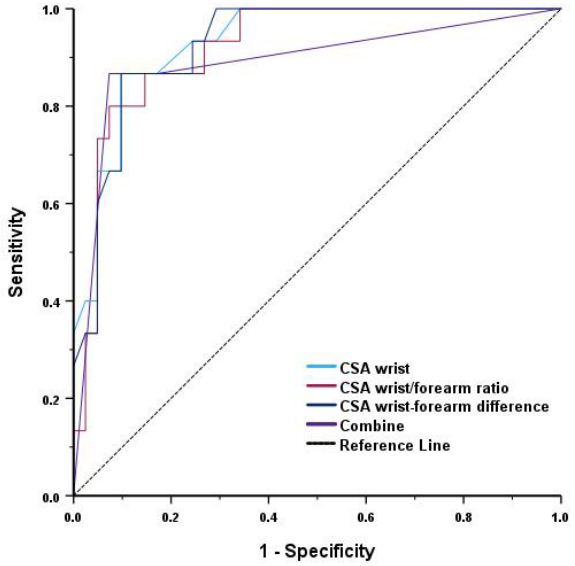

Figure 4. Receiver operating characteristic (ROC) curves with area under the curve of median nerve cross-sectional area (CSA) at the wrist, WFR (wrist-to-forearm ratio), and WFD (wrist-to-forearm difference) to assess severity of carpal tunnel syndrome

DISCUSSION

The results of this study indicate that the median nerve CSA-D, the WFR, and the WFD exhibit a substantial increase in CTS participants when compared to normal participants in Thailand. Additionally, the median nerve CSA-D, the WFR, and the WFD in CTS demonstrate a statistically significant moderate to strong positive correlation with disease severity as determined by the EDX.

The median nerve CSA-D (mm^2) of the study group (14.7 ± 5.9) was comparable to that of several studies which reported results ranging from 14.0 to 15.0 (6, 19, 20), however, Xu's (16.1 ± 0.8) (8) and Elnady's (18.4 ± 5.4) (7) studies reported larger averages. In contrast, the median nerve CSA-D in Billakota's study (12.6) (9), and El-Najjar's study (12.5 ± 3.4)(16) were smaller than our finding. The median nerve CSA-D (mm^2) in our control group (9.6 ± 2.4) is consistent with the findings of Phongamwong's study (9.4 ± 2.1) conducted in Thailand (21), while it differed slightly from previous studies (Hunderfund [8.6 ± 2.9], Webb [10.0 ± 2.3], Ratasvuori [7.0]) (5, 19, 20). Differences in demographic factors, including age in years (ours [52.5 ± 12.6], Webb [39.2 ± 14.2], Hunderfund [56 ± 16]) and ethnicity may influence the nerve CSA. Additionally, the different finger positions in different laboratories may also affect the nerve CSA. For example, some studies assessed the nerve CSA in finger flexion position (14, 22), while others evaluated it in finger extension position (20, 23). The measuring method used, which includes the trace and ellipsoid functions, may also have had an impact on the findings. Therefore, the nerve CSAs could differ between studies.

Table 4. Correlation between the median nerve CSA at wrist, wrist-to-forearm ratio (WFR), wrist-to-forearm difference (WFD) and severity of carpal tunnel syndrome

Parameters	Correlation coefficients[a]	*p*-value
CSA at wrist (mm^2)	0.678	<0.001*
WFR	0.713	<0.001*
WFD (mm^2)	0.743	<0.001*

[a]Spearman rank correlation coefficients, *statistically significant ($p < 0.05$)
CSA, cross-sectional area; mm^2, square millimeter; WFR, wrist-to-forearm ratio; WFD, wrist-to-forearm difference

Table 5. Correlation between ultrasound cross sectional area at wrist and electrodiagnostic parameters in carpal tunnel syndrome patients

Electrodiagnostic parameters of CTS	Correlation coefficient[a]	*p*-value
Latency SNAP	0.483	<0.001*
Amplitude SNAP	-0.358	0.012*
Latency CMAP	0.631	<0.001*
Amplitude CMAP	-0.479	<0.001*
NCV	-0.368	0.007*

[a]Pearson's correlation coefficient (r); *statistically significant ($p < 0.05$)
CTS, carpal tunnel syndrome; SNAP, sensory nerve action potential; CMAP, compound motor action potential; NCV, nerve conduction velocity (from wrist to forearm segment)

The average median nerve CSA-D (mm^2) in CTS severity grading by EDX in our study revealed values of 11.1 ± 2.5 for mild degree, 14.0 ± 4.6 for moderate degree, and 21.4 ± 5.6 for severe degree. Our results correspond with one previous study (12.0 ± 3.0 for mild, 15.0 ± 3.0 for moderate, 19.0 ± 6.0 for severe) (14) which applied the same CTS clinical and EDX criteria for diagnosis as ours. However, two other studies which used different criteria reported different findings (9-11 for mild, 11-13 for moderate, 12-15 for severe) (22, 24). Additionally, in the present study the median nerve CSA-D, WFR, and WFD exhibited statistically significant increases as the severity of CTS progressed according to the EDX grading. That correlation was comparable to those of the previous studies (6, 14, 16, 21, 25). However, one study reported no significant change in the

relationship between the median nerve CSA-D and the EDX severity grading (22), while others showed a weak correlation (5, 14). The discrepancy might arise from the classification of CTS severity grade, which was not consistent among the studies. A mild or moderate degree CTS involves mainly demyelination whereas a severe degree involves the axon. Patients with advanced degree CTS had greater CSA and more pronounced clinical manifestations compared to those with only demyelination (25, 26).

Because demographic factors can affect the nerve CSAs, the WFR and the WFD of the median nerve were the most suitable parameters to use as internal controls for detecting CTS. Moreover, direct measurement of the median nerve CSA at the wrist may not provide the most effective ultrasonographic criterion for diagnosis in CTS, especially for patients with other underlying pathologies, e.g., a patient with demyelinating hereditary sensorimotor neuropathy may have generalized enlargement of all nerves (27).

The WFR in CTS in our study group was 3.1 ± 1.4, which was statistically significantly different from the control group (1.7 ± 0.4). This outcome is comparable to those of earlier studies that measured the median nerve CSA at 12 cm proximal to the wrist or at mid-forearm level (Mhoon [2.3 ± 0.67], Hunderfund [3.1 ± 1.5]) (5, 6). However, in studies where the measurement was taken at the pronator quadratus (PQ) muscle, the ratio was 1.6 ± 0.1 (8, 23), which is lower than that of our control group. In CTS, the median nerve has a slight enlargement, reaching approximately 4 cm proximally from the wrist (28). Therefore, the WFR, calculated from the distal wrist and divided by the distal third of the forearm, would be reduced. Moreover, the intra- and inter-rater reliability rates were highest for visuals obtained at the wrist, with inter-rater reliability being fairly high at the mid-forearm and lowest at the PQ level (15). The median nerve CSA at the mid-forearm measurement appears to be more appropriate. While there are few studies on the median nerve WFD, our group found a significant difference ($p < 0.001$) compared to the control group. The value of our result is slightly lower than that in an earlier study (5).

In the present study, the WFR and the WFD (mm^2) cut-point values for CTS and non-CTS were 1.8 and 4.7. Our study's WFR was higher than Mhoon's study at 1.4 (6) and lower than Hunderfund's study at 2.4 (5). The sensitivity in Mhoon's study was high (97.0%) (6), similar to ours (89.3%), while it was medium in the Hunderfund's study (67.0%) (5). The median nerve WFR cut-points in our study were acceptable. Comparing the three values in our study, the cut-point value of the WFR and the WFD showed excellent sensitivity and accuracy (>80.0%), while the sensitivity (67.9%) and the accuracy (75.9%) of the median nerve CSA-D cut-point value were lower. The WFD also showed greater specificity (81.8%) compared to the WFR (71.4%). The WFD demonstrated superiority over the other methods for CTS screening, consistent with the findings of a previous study (5). Calculating the WFD may also be simpler than calculating the WFR. However, the CSA of nerves can differ among ethnic groups. The WFD values from our study may be applicable only to Thais but not to other ethnicities.

The sole ultrasonographic parameter to detect CTS demonstrated poor to intermediate sensitivity (47.0-70.0%), but the combination of two sonographic measurements, i.e., proximal CSA combined with volar bulging, yielded greater sensitivity (>90.0%) while maintaining the same specificity found in a previous study (29). Using multiple parameters for detection may enhance the screening process; however, because both the WFR and the WFD exhibited comparable good sensitivity (>80.0%) and accuracy (>80.0%), using both the WFR and the WFD may not result in better outcomes.

The median nerve CSA-D (mm^2) cut-point value for distinguishing CTS from non-CTS in this investigation was 10.7. That median nerve CSA-D cut-point value resembles previous studies (5, 7, 20). However, the mean CSA-D of the median nerve and the WFR in normal Thai individuals over 50 years of age were 10.5 mm^2, and 1.7, respectively (12). Ultrasonography should be used with caution when detecting CTS in the elderly (age > 50). In this study, the control group's WFR was 1.7, near to the CTS cut-point of 1.8. If the ratio is not clearly over the threshold limit, we recommend clinical diagnosis with EDX confirmation.

We analyzed the cut-point value to separate severe from non-severe cases because the median nerve CSA-D, WFR, and WFD significantly corre-

lated with the severity of EDX in our study. The cut-point values for detecting the median nerve CSA-D, the WFR, and the WFD in severe CTS in this study were 14.5 mm^2, 3.1, and 11.0 mm^2, respectively, demonstrating high sensitivity and specificity of more than 85.0%. These findings are consistent with Abrishamchi's study (CSA-D 15 mm^2, WFR 3), but that study had lower sensitivity and specificity (64.8-70.9%) than ours (14). Furthermore, research that used the median nerve CSA-D to distinguish CTS with moderate to severe degrees from none to mild degrees found 14.0 as a cut-point value, similar to ours, with high specificity (91.4%) but with low sensitivity (42.3%) (21). Although the median nerve CSA-D cut-point value appeared to be insufficient for screening across trials, it demonstrated great specificity in identifying patients with severe CTS.

CTS is generally diagnosed using clinical data and physical examination. The EDX is regarded as the reference standard for diagnosing and grading the severity of the disease, with sensitivities of 82.0-94.0% and specificities of 65.0-97.0% (2, 30). Surgery is the recommended treatment for severe cases. The cut-point values of the median nerve CSA measurements are essential for identifying severe CTS in locations where EDX equipment is not available and for patients who will not tolerate EDX investigation. Additionally, the US is painless, inexpensive, less time consuming, has no contraindications, and is easy to assess. It also enables observation of anatomical variation and nerve morphology which is also beneficial for treatment planning. According to a recent study, imaging is a supplemental tool to the basic clinical and EDX assessments of CTS, even if the combination of a typical clinical history and EDX results provides the most accurate diagnosis of this condition. Patients with unilateral CTS affecting the non-dominant hand, typical syndromes with negative electrophysiological findings, and atypical upper limb sensory syndromes are recommended to undergo ultrasonography (30). However, a standard protocol for scanning, including the positioning of the forearm and hand, the measurement site, and the tracing method, should be established.

Limitations

Our research has many limitations. Firstly, the absence of blinding the ultrasonographer to the diagnosis may have led to selection bias and may have affected the outcomes of the ultrasonography. Secondly, our control group did not coincide temporally with that of the study group. Third, there was an absence of inter-rater reliability evaluation. A recent study using ultrasonography scanning, however, did reveal good to excellent inter-rater reliability for median nerve assessment, suggesting that high-resolution ultrasonography is a reliable technique for evaluating the nerve CSA (12, 21). Forth, the study was conducted within the Thai ethnic group, so the cut-point values for identifying CTS are applicable only to that specific group. We utilized clinical criteria and EDX to diagnose CTS in accordance with AANEM guidelines; however, the ultrasound outcomes might have varied if other criteria had been employed in other laboratories. Fifth, when a patient has a CTS, the EDX may provide a false negative result, a situation which was not considered in this research. The cut-point values were not applicable to CTS patients who were diagnosed based on only their clinical presentation. Future research should improve the methodology, involve a larger prospective population, categorize participants into three severity groups for CTS, and should also include CTS patients with negative EDX findings.

CONCLUSIONS

Median nerve ultrasonography parameters are useful for identifying CTS in a healthy Thai population. The findings demonstrate that the WFR and the WFD, which are not dependent on demographic factors, are appropriate additional variables for detecting CTS with positive EDX. Cut-points of all three measures demonstrated good sensitivity and moderate to high specificity. The ultrasonography parameters were also able to distinguish severe from mild to moderate degrees. A significant moderate to strong positive correlation was found between the median nerve CSA-D, WFR, and WFD and the CTS severity by EDX. The diagnostic recommendations are primarily based on clinical and physical examinations, with ultrasound serving as a complementary method.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

REFERENCES

1. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of carpal tunnel syndrome in a general population. JAMA. 1999;282:153-8.
2. Dahlin L, Zimmerman M, Calcagni M, Hundepool CA, van Alfen N, Chung KC. Carpal tunnel syndrome. Nat Rev Dis Primers. 2024;10:37. PubMed PMID: 38782929.
3. Werner R, Andary M. Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve. 2011;44:597-607.
4. Miller L, Hammert W, Rekant M, Fowler J. Diagnostic accuracy of neuromuscular ultrasound vs. electrodiagnostic studies for carpal tunnel syndrome: Systematic Review and Meta-analysis of Paired Accuracy Studies. Hand (N Y). 2024:15589447241278972. PubMed PMID: 39324685
5. Hunderfund A, Boon A, Mandrekar J, Sorenson E. Sonography in carpal tunnel syndrome. Muscle Nerve. 2011;44:485-91.
6. Mhoon J, Juel V, Hobson-Webb L. Median nerve ultrasound as a screening tool in carpal tunnel syndrome: correlation of cross-sectional area measures with electrodiagnostic abnormality. Muscle Nerve. 2012;46:871-8.
7. Elnady B, Rageh E, Ekhouly T, Fathy S, Alshaar M, Fouda E, et al. Diagnostic potential of ultrasound in carpal tunnel syndrome with different etiologies: correlation of sonographic median nerve measures with electrodiagnostic severity. BMC Musculoskelet Disord. 2019;20:634. PubMed PMID: 31884951
8. Xu C, Zhou Y, He Z, Liu W, Zou M, Sun Y, et al. Difference and ratio of the cross-sectional area of median nerve at the carpal tunnel and the pronator quadratus muscle in diagnosing carpal tunnel syndrome: a cross-sectional study. Ann Transl Med. 2022;10:340. PubMed PMID: 35433935
9. Billakota S, Hobson-Webb LD. Standard median nerve ultrasound in carpal tunnel syndrome: A retrospective review of 1,021 cases. Clin Neurophysiol Pract. 2017;2:188-91.
10. Burg E, Bathala L, Visser LH. Difference in normal values of median nerve cross-sectional area between Dutch and Indian subjects. Muscle Nerve. 2014;50: 129-32.
11. Tan C, Razali S, Goh K, Shahrizaila N. Influence of demographic factors on nerve ultrasound of healthy participants in a multiethnic Asian population. J Med Ultrasound. 2021;29:181-6.
12. Ngernprasertsiri S, Puprasert C, Wimonwattrawatee P. Reference values of nerve cross-sectional area obtained by ultrasound in the upper extremity correlated with electrodiagnosis in Thai adults. Biomedical Sciences and Clinical Medicine. 2023;62:158-68.
13. Borire AA, Hughes AR, Lueck CJ, Colebatch JG, Krishnan AV. Sonographic differences in carpal tunnel syndrome with normal and abnormal nerve conduction studies. J Clin Neurosci. 2016;34:77-80.
14. Abrishamchi F, Zaki B, Basiri K, Ghasemi M, Mohaghegh M. A comparison of the ultrasonographic median nerve cross-sectional area at the wrist and the wrist-to-forearm ratio in carpal tunnel syndrome. J Res Med Sci. 2014;19:1113-7.
15. Junck A, Escobedo E, Lipa B, Cronan M, Anthonisen C, Poltavskiy E, et al. Reliability assessment of various sonographic techniques for evaluating carpal tunnel syndrome. J Ultrasound Med. 2015;34:2077-88.
16. El-Najjar A, Abu-Elsoaud A, Sabbah D, Zeid A. Emerging role of ultrasonography in the diagnosis of carpal tunnel syndrome: Relation to risk factors, clinical and electrodiagnostic severity. The Egyptian Rheumatologist. 2021;43:341-5.
17. Linehan C, Childs J, Quinton A, Aziz A. Ultrasound parameters to identify and diagnose carpal tunnel syndrome. A review of the literature. Australas J Ultrasound Med. 2020;23:194-206.
18. Chen S, Andary M, Buschbacher R, Del Toro D, Smith B, So Y, et al. Electrodiagnostic reference values for upper and lower limb nerve conduction studies in adult populations. Muscle Nerve. 2016;54:371-7.
19. Hobson-Webb LD, Massey JM, Juel VC, Sanders DB. The ultrasonographic wrist-to-forearm median nerve area ratio in carpal tunnel syndrome. Clin Neurophysiol. 2008;119:1353-7.
20. Ratasvuori M, Sormaala M, Kinnunen A, Lindfors N. Ultrasonography for the diagnosis of carpal tunnel syndrome: correlation of clinical symptoms, cross-sectional areas and electroneuromyography. J Hand Surg Eur Vol. 2022;47:369-74.
21. Phongamwong C, Soponprapakorn N, Kumnerddee W. Determination of electrophysiologically moderate and severe carpal tunnel syndrome: ultrasonographic measurement of median nerve at the wrist. Ann Rehabil Med. 2017;41:604-9.
22. Mohammadi A, Afshar A, Etemadi A, Masoudi S, Baghizadeh A. Diagnostic value of cross-sectional area of median nerve in grading severity of carpal tunnel syndrome. Arch Iran Med. 2010;13:516-21.
23. Vögelin E, Mészàros T, Schöni F, Constantinescu MA. Sonographic wrist measurements and detection of anatomical features in carpal tunnel syndrome. ScientificWorldJournal. 2014;2014:657906. PubMed PMID: 24672350.
24. Zhang L, Rehemutula A, Peng F, Yu C, Wang TB, Chen L. Does the ratio of the carpal tunnel inlet and outlet cross-sectional areas in the median nerve reflect carpal tunnel syndrome severity? Neural Regen Res. 2015;10:1172-6.
25. Kohls M, Mak A, Fowler J. Ultrasound cross-sectional area in median nerve axonal loss and demyelina-

tion in carpal tunnel syndrome. J Hand Microsurg. 2024;16(2):100045. PubMed PMID: 38855512.
26. Wijntjes J, Borchert A, van Alfen N. Nerve Ultrasound in traumatic and iatrogenic peripheral nerve injury. Diagnostics (Basel). 2020;11;30. PubMed PMID: 33375348
27. Martinoli C, Schenone A, Bianchi S, Mandich P, Caponetto C, Abbruzzese M, et al. Sonography of the median nerve in Charcot-Marie-Tooth disease. AJR Am J Roentgenol. 2002;178:1553-6.
28. Thomas P, Fullerton P. Nerve fibre size in the carpal tunnel syndrome. J Neurol Neurosurg Psychiatry. 1963;26:520-7.
29. Koroglu O, Kesikburun S, Adiguzel E, Taskaynatan M, Ozgul A. Estimating the most accurate sonographic measurement in the diagnosis of carpal tunnel syndrome: Which is the best? Turk J Phys Med Rehabil. 2019;65:177-83.
30. Hannaford A, Paling E, Silsby M, Vincenten S, van Alfen N, Simon NG. Electrodiagnostic studies and new diagnostic modalities for evaluation of peripheral nerve disorders. Muscle Nerve. 2024;69:653-69.

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Correlation and Agreement Between the Occupational Vision Screener and Ophthalmologic Tests in Visual Performance Assessment of Surgical Health Professionals

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ABSTRACT

OBJECTIVE This study aims to evaluate the correlation and agreement between occupational vision tests and standard ophthalmological examinations across five dimensions of visual performance.

METHODS Fifty-three participants underwent assessments for visual acuity (VA), red-green color vision, stereoscopic depth, and phoria using both the Titmus occupational vision screener and ophthalmologist-administered tests, including the Early Treatment Diabetic Retinopathy Study (ETDRS) chart for VA, Farnsworth D-15 for color vision, Stereotest-Circles for stereoscopic depth, and the cover-uncover test for phoria. To compare the correlation or agreement of each parameter between the two methods, correlation coefficients were used to evaluate VA and stereoscopic depth perception, Kappa analysis for color blindness, phoria and astigmatism. Statistical significance was set at $p < 0.05$.

RESULTS Test results were finalized with 53 participants, mean age of 29.4 years. A majority of the participants (62.30%) reported a history of prior and/or present use of visual aids. The assessment of visual capacity demonstrated a good correlation between occupational stereoscopic depth and Stereotest-circles (0.5997, $p < 0.001$) and a moderate correlation between the Occupational best corrected VA and ETDRS best corrected VA (maximum 20/20) (0.4616, $p < 0.001$). Color vision screening showed a high level of statistical agreement with a kappa value of 1.00. However, the results for phoria and astigmatism were inconsistent with only left-eye astigmatism demonstrating statistical significance ($p = 0.047$), but with only a fair Kappa value (0.21).

CONCLUSIONS Occupational vision tests showed strong to moderate correlation for stereoacuity and visual acuity and high agreement of color with standard methods. These tests are useful for visual screening of surgical professionals. Further extensive examinations of other parameters and with a wider variety of participants are required for a more comprehensive assessment of visual capacity related to specific job tasks.

KEYWORDS stereo acuity, visual acuity, vision test, occupation, color vision

INTRODUCTION

Visual performance is one of the most important functions in work activities and daily life. Key aspects of eye performance include visual acuity (VA), which ensures clear vision in various job tasks and is essential for responding effectively in urgent situations. Stereoscopic depth is crucial for determining the distance to objects, such as when driving or operating a moving object or device. The perception of color plays a role in distinguishing and recognizing different shades and hues. Some careers require optimal visual performance across several areas to ensure fitness for duty, such as driving, fire-fighting, and airplane piloting (1-3).

Physicians encounter specific occupational risks (4) which could potentially impact the safety of both patients and healthcare personnel. The diverse range of medical specialties introduces unique job characteristics for each specialty. For example, surgically skilled physicians, e.g., surgeons, orthopedists, ophthalmologists, otolaryngologists, and obstetric gynecologists, rely heavily on visual capabilities (5). Their work involves activities that require sustained focus, visuospatial perception, and coordination (6). Their work also often demands sustained concentration and meticulous attention to detail. Evaluating visual capacity is crucial in determining an individual's preparedness for work (7). However, assessing the entire range of key factors related to their job performance can require significant time.

Ophthalmological assessments generally include evaluation of multiple ocular functions (8, 9). For example, VA is measured with a Snellen or ETDRS chart to quantify the smallest resolvable optotype by each eye. Phoria is evaluated using the cover-uncover test or prism bars to detect phoria or strabismus, both of which may cause eyestrain or diplopia during sustained focus. Depth perception is usually tested using the fly or butterfly stereotests, which use polarized images to assess 3D depth perception. Color vision is assessed with pseudoisochromatic plates like the Ishihara and Hardy-Rand-Rittler (HRR) tests. The Farnsworth D-15 test is additionally employed to evaluate both red-green and blue-yellow deficiencies and to grade their severity. Astigmatism is detected using an auto-refractometer for objective refractive error measurement. Visual field is measured by automated perimeters, e.g., a Humphrey visual field analyzer, to detect vision loss, crucial in visually demanding tasks.

The occupational vision test is one of the tools employed to evaluate preparedness for visual work which has become more widely available in occupational medicine clinics. The primary objective of this test is to match the job requirements with the job category (10). The tool is a compact portable device capable of evaluating seven aspect visual parameters: VA, phoria, stereoscopic depth perception, vertical and horizontal phoria, color blindness, astigmatism, visual field, and binocular vision (11). Each of these areas is crucial for assessing visual performance. Although standard ophthalmologic tools are often permanently installed in clinics and require time, trained personnel and a controlled environment to complete a full assessment, the occupational vision screener device is portable, making it practical for proactive screening in various settings such as communities, primary care clinics, and workplaces. It enables quick, one-stop screening of multiple visual parameters outside a hospital setting and requires fewer operators to run. Vision screening plays a vital role in assessing fitness for duty, e.g., professions such as dentistry and surgery require precise perceptual and visual skills to perform procedures effectively (12, 13). Similarly, motor vehicle driving demands adequate VA and visual field to ensure safety during both daytime and nighttime conditions. Previous studies have demonstrated that visual impairments are significantly associated with an increased risk of road traffic accidents (14). However, a knowledge gap persists regarding the consistency of these tools in evaluating job tasks that do not fit into existing categories. If occupational vision tests are shown to correlate well with standard vision tests, they might be adopted more broadly, thus reducing the time and resources needed for evaluating healthcare workers. Since no prior study has assessed the accuracy of this test or its agreement with standard examinations, the present study was conducted to determine the correlation and agreement between occupational vision tests and standard ophthalmological examinations across five dimensions of visual performance: VA, color vision, phoria, stereoscopic depth perception, and astigmatism among surgical health professionals.

METHODS

Study Design and Population

The cross-sectional study was conducted in June 2023 at the teaching hospital in Chiang Mai, Thailand. The sample size was determined using the n4Studies program, based on the infinite population proportion formula by Daniel (15) The parameters used included a prevalence (P) of 0.29, based on a study by Alhusuny et al. (16), a delta (d) of 0.2, an alpha (α) of 0.05, and a Z (0.975) value of 1.959964. The calculated minimum required sample size was 20 participants. To ensure adequate power and to account for potential dropouts or missing data, we increased the sample size by 150.00%, resulting in a final sample of 50 participants. We recruited a total of 57 newly trained first-year physicians whose jobs involved surgical procedures. The study included individuals who consented to participate and who could communicate verbally. The study enrollment flow diagram is shown in Figure 1.

Data collection

The study was divided into two parts. Part 1 involved a structured questionnaire for collecting general demographic data, e.g., age, sex, height, weight, underlying health conditions, and visual health-related information such as eyeglass use, history of eye surgery, and use of artificial tears. Part 2 involved visual performance screening and ophthalmologic diagnostics. The participants provided demographic information and underwent eye examinations to obtain data across five aspects: VA, color vision, phoria, stereoscopic depth perception, and total astigmatism. The data collection was conducted over two days. On the first day, occupational health screenings were performed, and on the second day, ophthalmologist examinations were conducted. This scheduling was designed to reduce eye fatigue from prolonged periods of eye examination. The Titmus V4 Vision Screener (Titmus LLC, Honeywell International Inc., Charlotte, NC, USA) was conducted by a single occupational medicine physician in a private examination room and included evaluation of phoria, depth perception ranges from 400 to 10 seconds of arc, VA (both far and near, binocular and monocular), color vision, and visual field in this sequence. Astigmatism was assessed separately using a Visiolite VT1 Vision Screener (Depisteo LLC, Atlanta, GA, USA). The interpretation for color vision, phoria, and total astigmatism followed the devices' instructions, with details provided in the supplementary file. After the evaluation using occupational eye health screening tools, an ophthalmologist evaluated the majority of the elements using standard methods, with the exception of binocular vision, visual field, and near VA. Ophthalmologist-standard tools were also used to examine the same five aspects: 1) VA assessments were conducted using an Early Treatment Diabetic Retinopathy Study (ETDRS) Chart, with data presented as decimal scores and converted to logMAR units. The ETDRS chart is the accepted benchmark in clinical trials owing to its logarithmic progression and high test-retest reliability (17). 2) Color blindness examinations were performed via the Farnsworth D15 test (Good-Lite Co., Elgin, IL, USA), a high specificity tool capable of distinguishing protan and deutan defects and grading mild to severe deficiency (18). Abnormal results were indicated

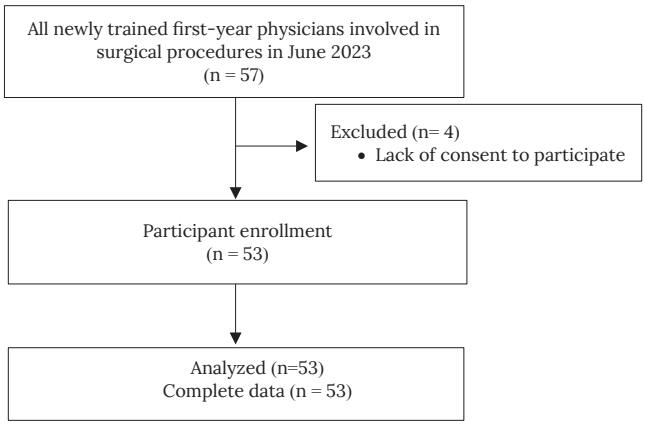

Figure 1. Study enrollment flow diagram

by more than 2 crossing lines in a diagram. 3) Stereoscopic depth perception was evaluated using stereotest circles (Stereo Optical Co., Inc., Ltd., Chicago, IL, USA), with results ranging from 800 to 40 seconds of arc. This tool was selected for its minimal monocular cues, validated sensitivity to sub-arc-second disparities, and widespread use in both research and clinical settings due to its high specificity (19). 4) Phoria was assessed using the ophthalmologist's cover-uncover test, which has demonstrated high specificity (20). Phoria was indicated when the occluded eye deviated and then returned to a straight position upon removal of the occlude. 5) Measurements for total astigmatism were conducted using an Auto-refractometer (Nidek Co. Ltd., Aichi, Japan) and categorized into four groups: none, direct astigmatism (vertical meridian is steeper), inverse astigmatism (horizontal meridian is steeper), and oblique astigmatism. Ophthalmological diagnostic tests were conducted at an ophthalmology clinic under standard clinical settings. All tests were conducted by trained personnel with experience in operating each device. To minimize operator bias and ensure standardization, the same examiner conducted the same test for all participants. Equipment setup and calibration followed clinic protocols and manufacturer recommendations.

Statistical analysis

Descriptive analysis was used to determine frequencies, mean averages, and proportions of categorical and continuous variables. To compare the results between the occupational health vision screening tools and those used by ophthalmologists, pairwise correlation analysis was employed to evaluate the correlation of best corrected VA and stereo depth values. A correlation coefficient close to +1 indicates a strong positive linear association, while a value near −1 signifies a strong negative linear association. Conventionally, values >0.7 are classified as 'strong,' 0.5–0.7 as 'good,' 0.3–0.5 as 'fair or moderate,' and <0.3 as a 'weak' correlation (21). The level of inter-rater agreement in color vision assessment, phoria, and astigmatism was evaluated using Cohen's Kappa to measure reliability for qualitative (categorical) items was interpreted as follows (22): < 0.00 was classified as 'poor', 0.00–0.20 as 'slight', 0.21–0.40 as 'fair', 0.41–0.60 as 'moderate', 0.61–0.80 as 'substantial', and 0.81–1.00 as almost perfect. The statistical significance level was set at a $p < 0.05$ and the confidence interval at 95%. STATA version 16.0 (StataCorp LLC, College Station, TX, USA) was used to assess and evaluate all the data.

Ethical considerations

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai university, Thailand (study approval code: COM-2565-09077). The study was reported according to the STROBE guidelines.

RESULTS

A total of 53 first-year physicians who had recently started their employment at the medical school participated in the study, representing a 92.98% response rate. Most participants (92.40%) reported no evidence of any underlying health problems before taking part in this study. The majority of participants (49.00%) relied solely on glasses to correct their vision, followed by contact lenses (7.60%), and a combination of both glasses and contact lenses (5.70%). Of the participants,

Table 1. The Characteristics of the participants (N = 53)

Characteristics	n (%)
Age (years), mean±SD	29.4±2.8
Weight (kg), mean± SD	66.9±2.8
Height (cm), mean±SD	168.6±9.7
Gender	
Female	18 (34.0)
Male	35 (66.0)
Underlying health conditions[a]	
Yes	4 (7.6)
No	49 (92.4)
Current Use Visual aids	
No	20 (37.7)
Glasses only	26 (49.0)
Contact lens only	4 (7.6)
Glasses and contact lens	3 (5.7)
Use of artificial tears	
Yes	16 (30.2)
No	37 (69.8)
History of refractive surgery	
No	43 (81.0)
Laser *In situ* keratomileusis (LASIK)	3 (5.7)
Photorefractive keratectomy (PRK)	2 (3.8)
Refractive lenticule extraction (ReLEx)/ small incision lenticule Extraction (SMILE)	3 (5.7)
Implantable collamer lens	2 (3.8)

[a]Underlying health conditions: 3 cases of allergic rhinitis and 1 case of dyslipidemia

Table 2. Compared visual performance assessments (N = 53)

Parameters	Occupational health vision exams n (%)	Ophthalmologist n (%)
Color vision		
Normal	52 (98.1)	52 (98.1)
Abnormal	1 (1.9)	1 (1.9)
Phoria		
Far horizontal phoria		
No phoria	31 (58.5)	51 (96.2)
Phoria is present	22 (41.5)	2 (3.8)
Far vertical phoria		
No phoria	51 (96.2)	53 (100.0)
Phoria is present	2 (3.8)	0 (0.0)
Near horizontal phoria		
No phoria	40 (75.5)	50 (94.3)
Phoria is present	13 (24.53)	3 (5.7)
Near vertical phoria		
No phoria	49 (92.45)	53 (100.0)
Phoria is present	4 (7.55)	0 (0.0)
Astigmatism, left eye		
None	19 (35.8)	31 (58.5)
Direct astigmatism	9 (17.0)	1 (1.9)
Inverse astigmatism	15 (28.3)	20 (37.7)
Oblique astigmatism	10 (18.9)	1 (1.9)
Astigmatism, right eye		
None	25 (47.2)	16 (30.2)
Direct astigmatism	10 (18.9)	1 (1.9)
Inverse astigmatism	11 (20.7)	34 (64.1)
Oblique astigmatism	7 (13.2)	2 (3.8)
Parameters	**Occupational health vision exams (Mean±SD)**	**Ophthalmologist (Mean±SD)**
Best-Corrected Visual Acuity		
Distance logMAR VA, both eyes	0.1061±0.1779	N/A
Distance logMAR VA, left eye	0.1235±0.1515	0.0150±0.0507
Distance logMAR VA, right eye	0.1504±0.2063	0.0215±0.0778
Near logMAR VA, both eyes	0.0447±0.1101	N/A
Near logMAR VA, left eye	0.1205±0.1701	N/A
Near logMAR VA right eye	0.1232±0.1446	N/A
Stereoscopic depth		
Seconds of arc	84.3±98.6	43.6±9.4
Seconds of arc (median, P25, P75)	50,20,100	40,40,40

N/A, not applicable; SD, standard deviation

37.70% required no visual aids. A high proportion of participants (69.80%) needed no artificial tears and denied a history of refractive surgery (81.00%). Additional information regarding participant characteristics is provided in Table 1. Table 2 shows details of the visual performance assessments of the individuals who underwent evaluations for each test parameter.

The data was used to compare assessments performed by ophthalmologists to those carried out during occupational health vision examinations, as presented in Table 3 and Table 4. Color vision screening showed a high level of agreement between the two measurements, with a kappa value of 1.00 and 100.00% agreement. Phoria assessment using the occupational health vision exam showed poor, non-significant agreement. For astigmatism, only left-eye astigmatism demonstrated fair agreement, with a Kappa value of 0.21 and a statistically significant *p*-value of

Table 3. The agreement of outcomes in each visual performance assessment

Occupational health vision exams	Visual capacity assessments by ophthalmologists				
	Abnormal	Normal	Total	% Agreement	Kappa (*p*-value)
Farnsworth Test					
Color vision screening[+]					
Abnormal	1	5	1	100%	1.000
Normal	0	52	52		(<0.001)
Total	1	52	53		
Cover-uncover test					
Far phoria[+]					
Abnormal	1	15	16	69.81%	0.050
Normal	1	36	67		(0.267)
Total	2	51	53		
Near phoria[+]					
Abnormal	1	4	5	88.68%	0.190
Normal	2	46	48		(0.072)
Total	3	50	53		
Right astigmatism					
Astigmatism, right eye[+]					
Abnormal	20	8	28	25.83%	0.035
Normal	17	8	25		(0.393)
Total	37	16	53		
Left astigmatism					
Astigmatism, left eye[+]					
Abnormal	15	17	34	58.49%	0.210
Normal	5	14	19		(0.047)
Total	22	31	53		

[+]Analyzed by kappa analysis

0.047. Table 4 shows the correlation analysis of visual capacity, examining the association between variables evaluated using the occupational vision test and the standard techniques performed by ophthalmologists. Correlations that demonstrated statistical significance were seen between occupational stereoscopic depth and stereotest-circles test (0.5997, $p < 0.001$), indicating a good correlation. Additionally, a moderate correlation was found between occupational VA and ETDTS VA (maximum 20/20) (0.4616, $p < 0.001$).

Table 4. Correlations of visual performance between the assessments by Occupational health vision examination and ophthalmologist

	Correlation	*p*-value
Occupational stereoscopic depth vs. stereotest-circles	0.5997	< 0.001
Occupational best corrected VA vs. ETDRS best corrected VA (maximum 20/20)	0.4616	< 0.001

ETDRS, Early Treatment Diabetic Retinopathy Study

DISCUSSION

The studies indicated statistically significant correlation in visual performance between assessments conducted using occupational health vision examinations and conducted by ophthalmologists. Specifically, correlations were observed in stereoscopic depth and the stereotest circles, as well as occupational best-corrected visual acuity and ETDRS best-corrected VA (maximum 20/20), demonstrating strong and moderate correlation strengths of 0.5997 and 0.4616, respectively. The evaluation of stereoscopic depth in minutes of arc revealed median measurements of 50 seconds of arc with the occupational health vision assessment and 40 seconds of arc with the stereotest-circles performed by the ophthalmologist. Participants demonstrated superior stereoacuity with both tools, surpassing the threshold

of less than 60 seconds of arc observed in prior studies (23, 24). Based on the significant correlation, the occupational vision test can provide good correlation results to assess stereoacuity and to determine the level of stereoscopic depth. However, the use of stereotest-circles was restricted to the best stereoacuity measurement of 40 seconds of arc (25). Additionally, monocular cues in the easier test items may have partially influenced stereoscopic depth perception, allowing participants to respond without truly perceiving depth (26). The occupational vision screening tool offers an extensive assessment of depth perception, reaching up to 10 seconds of arc, and may be less affected by monocular cues. Although our results do not determine the appropriate passing threshold for the occupational health vision test in surgical professionals, meeting the minimum stereoscopic depth criteria in this test suggests a high level of stereoscopic depth perception. A good stereo depth function could enhance surgical skills, despite ongoing debates regarding the level of stereopsis required for satisfactory performance (23, 27).

We computed VA for both eyes and compared it with the best-corrected VA as per the ETDRS standard, with a maximum of 20/20. The correlation between the two tests demonstrated statistical significance, but with moderate strength. A previous study which developed a new VA test and compared it with standard tools, found that the new VA test demonstrated higher correlation and lower error rates in right eyes (28). A previous study found that occupational health vision exams had a positive predictive value of 20.40% and a specificity level of 64.30% for visual impairment screening, suggesting that there may be many false positives which require additional investigation (29). In addition, other studies have indicated that VA often provides worsen results when used with the Landolt C chart, commonly employed in occupational health vision examinations, compared to the Snellen chart. However, the observed discrepancies were minimal (30-33). In our study, the majority of the participants did not use artificial tears (69.80%) and currently used visual aids (62.30%). The use of glasses or contact lenses to correct refractive errors may affect accommodative and binocular visual functions (34), potentially affecting test outcomes. Additionally, tear film instability caused by dry eye can lead to a decline in VA. Artificial tears, as a modifiable intervention, may offer both immediate and long-term benefits for VA improvement (35).

The color vision assessment in the occupational health vision examination demonstrated a high level of agreement. This result was expected, as the assessment details of this test were a condensed version of the Ishihara color vision test. Although the color vision assessment in the occupational health vision examination is limited to detecting congenital red-green color blindness, it is sufficient for pre-placement screening. In addition, nearly all Thai physicians have had color vision examinations before beginning their medical study (36). Based on our results, this color vision assessment might be used as a screening confirmation test for color vision problems among interns, especially, as in the present study, physicians with surgical skills. Other more-specific tools, such as the Hardy-Rand-Rittler (HRR) pseudoisochromatic test, Farnsworth arrangement test, and L'Anthony test D-15 test (37, 38), may help to identify more specific details of color blindness and its severity.

The inconsistent results for phoria and astigmatism found in this study may be partly due to chance. One possible explanation for the non-significant result for phoria is that the occupational health vision screener requires fixed convergence to engage with the screen, which may influence phoria adaptation (39). Future studies should consider alternative designs to minimize this effect.

This study demonstrated strength as a pioneering study intended to support the practical application of occupational vision tests by evaluating the correlation between these tests and standard tests performed by ophthalmologists. Stereo depth as measured by the device may serve as a reliable standard for screening fine binocular function and as rule-out tests for subtle binocular abnormalities. In contrast, VA and color vision measurements are most effective for ruling out gross deficits prior to confirmation with further standard assessments.

This study does, however, have certain limitations. Although the study attempted to reduce operator bias by having the same examiner conduct all tests, the lack of blinding could still have

introduced observer bias, where prior knowledge of a participant's status may have unintentionally influenced the assessment. Another limitation is the study design, as the cross-sectional study was conducted in the specific context of a teaching hospital. The recruitment of participants may have led to a healthy participant effect due to selection bias, despite exceeding the calculated required study population size. As a pilot study, it is appropriate only for pre-placement assessments of newly trained interns in departments requiring surgical skills. Future studies should include more diverse participants, be conducted over longer periods of employment, and focus on specific surgical procedures that may influence visual fatigue. Healthcare professionals may experience visual fatigue not only during conventional surgery but also during specialized procedures such as robotic surgery (40). Establishing visual performance standards for more specialized surgical procedures will? require additional research.

CONCLUSIONS

The applicability of the Occupational Vision Test appears to depend on which specific parameters are being evaluated. Phoria exhibited high specificity, whereas stereoscopic depth and the best-corrected VA test for both eyes showed strong and moderate correlation with standard methods, respectively. The color blindness test demonstrated high agreement with standard tests. These findings highlight its potential for optimizing visual assessment of surgical health professionals. Future studies that include more diverse participant populations and which provide more information about specific surgical procedures could improve understanding of how suitable different occupational vision tests are for various surgical uses and clinical applications.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ADDITIONAL INFORMATION

Author contributions

P.A.: conceptualization, formal analysis, investigation, methodology, resources, visualization, writing - original draft, writing - review & editing; J.P.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, writing - original draft, writing - review & editing; P.U.: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, validation, writing - review & editing; W.S.: formal analysis, methodology, software, validation, writing - review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 3.0 in order to improve the language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. National Fire Protection Association. NFPA 1582, Standard on comprehensive occupational medical program for fire departments. Quincy, MA, USA: UK; 2022.
2. Driver and Vehicle Licensing Agency [Internet]. Assessing fitness to drive: a guide for medical professionals. 2016. [cite 2025 Jan 31]. Available from: https://www.gov.uk/government/publications/assessing-fitness-to-drive-a-guide-for-medical-professionals
3. Matthews M, Stretanski M. Pilot Medical Certification. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Michael Stretanski declares no relevant financial relationships with ineligible companies. 2024.
4. Ryu R, Behrens P, Malik A, Lester J, Ahmad C. Are we putting ourselves in danger? Occupational hazards and job safety for orthopaedic surgeons. J Orthop. 2021;24:96-101.
5. Hirata T. Simple, near, visual perception test for microsurgeon -parallelism-. Clinical and Experimental Dental Research. 2022;9:165-70.

6. Gazit N, Ben-Gal G, Eliashar R. Using job analysis for identifying the desired competencies of 21st-Century surgeons for improving trainees selection. J Surg Educ. 2023;80:81-92.
7. Zheng B, Jiang X, Bednarik R, Atkins MS. Action-related eye measures to assess surgical expertise. BJS Open. 2021;5(5):zrab068. PubMed PMID: 34476467
8. Yanoff M, Duker J. Ophthalmology E-Book: Elsevier Health Sciences; 2018.
9. Mukherjee P. Clinical examination in ophthalmology-e-book: clinical examination in ophthalmology-E-Book: Elsevier Health Sciences; 2016.
10. Good G, Weaver J, Augsburger A. Determination and application of vision standards in industry. Am J Ind Med. 1996;30:633-40.
11. McAlister W, Peters J. The validity of Titmus Vision testing results. Mil Med. 1990;155:396-400.
12. Dimitrijevic T, Kahler B, Evans G, Collins M, Moule A. Depth and distance perception of dentists and dental students. Oper Dent. 2011;36:467-77.
13. Al-Saud LM, Mushtaq F, Mirghani I, Balkhoyor A, Keeling A, Manogue M, et al. Drilling into the functional significance of stereopsis: the impact of stereoscopic information on surgical performance. Ophthalmic Physiol Opt. 2017;37:498-506.
14. Tamenti G, Rasengane T, Mashige K. The association between road traffic accidents and visual functions: A systematic review and meta-analysis. Afr J Prim Health Care Fam Med. 2024;16:e1-e10. PubMed PMID: 39221740
15. Daniel W, Cross C. Biostatistics: a foundation for analysis in the health sciences: John Wiley & Sons; 2018.
16. Alhusuny A, Cook M, Khalil A, Johnston V. Visual symptoms, neck/shoulder problems and associated factors among surgeons performing Minimally Invasive Surgeries (MIS): A comprehensive survey. Int Arch Occup Environ Health. 2021;94:959-79.
17. Ferris F, 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982;94:91-6.
18. Read J, Rafiq S, Hugill J, Casanova T, Black C, O'Neill A, et al. Characterizing the Randot Preschool stereotest: Testability, norms, reliability, specificity and sensitivity in children aged 2-11 years. PLoS One. 2019;14:e0224402. PubMed PMID: 31697704
19. Cole B, Orenstein J. Does the Farnsworth D15 test predict the ability to name colours? Clin Exp Optom. 2003;86:221-9.
20. Mori D, Kuchhangi A, Tame J, Cooper K, Hajkazemshirazi L, Indaram M, et al. Evaluation of a novel virtual reality simulated alternate cover test to assess strabismus: a prospective, masked study. Am J Ophthalmol. 2025;269:266-72.
21. Hazra A, Gogtay N. Biostatistics series module 6: correlation and linear regression. Indian J Dermatol. 2016;61:593-601.
22. Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-74.
23. Biddle M, Hamid S, Ali N. An evaluation of stereoacuity (3D vision) in practising surgeons across a range of surgical specialities. Surgeon. 2014;12:7-10.
24. Odell N, Hatt S, Leske D, Adams W, Holmes J. The effect of induced monocular blur on measures of stereoacuity. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2009;13:136-41.
25. Deepa B, Valarmathi A, Benita S. Assessment of stereo acuity levels using random dot stereo acuity chart in college students. J Family Med Prim Care. 2019;8:3850-3.
26. Hahn E, Comstock D, Durling S, MacCarron J, Mulla S, James P, et al. Monocular clues in seven stereotests. Dalhousie Medical Journal. 2010;37(1).
27. Wong N, Stokes J, Foss A, McGraw P. Should there be a visual standard for ophthalmologists and other surgeons? Postgraduate Medical Journal. 2010;86:354-8.
28. Di Foggia E, Stoll N, Meunier H, Rimele A, Ance P, Moreau PH, et al. A new visual acuity test on touchpad for vision screening in children. Int J Ophthalmol. 2020;13:1436-42.
29. Kumar N, Karvonen-Gutierrez C, Musch D, Harlow S, Burnett D, Valenzuela C, et al. Validity of the Titmus Vision Screener: A Comparison with the Snellen Chart. Journal of Ophthalmic Science. 2019;2:35-43.
30. Chaikitmongkol V, Nanegrungsunk O, Patikulsila D, Ruamviboonsuk P, Bressler NM. Repeatability and agreement of visual acuity using the ETDRS number chart, Landolt C Chart, or ETDRS alphabet chart in eyes with or without sight-threatening diseases. JAMA Ophthalmol. 2018;136:286-90.
31. Lai Y-H, Wu H-J, Chang S-J. A reassessment and comparison of the Landolt C and tumbling E charts in managing amblyopia. Scientific Reports. 2021;11:18277.
32. Becker R, Gräf M. [Landolt C and snellen e acuity: differences in strabismus amblyopia?]. Klin Monbl Augenheilkd. 2006;223:24-8.
33. Teerasantipun C, Pichetweerachai W, Theerakul T, Chaiwong W, Kunanusont C. Validity of vision screener among workers in a private hospital in the northern part of Thailand. The Bangkok Medical Journal. 2019;15:140.
34. Jimenez R, Martinez-Almeida L, Salas C, Ortiz C. Contact lenses vs spectacles in myopes: is there any difference in accommodative and binocular function? Graefes Arch Clin Exp Ophthalmol. 2011;249:925-35.
35. Nilforoushan MR, Latkany RA, Speaker MG. Effect of artificial tears on visual acuity. Am J Ophthalmol. 2005;140:830-5.
36. Tan TF, Grzybowski A, Ruamviboonsuk P, Tan ACS. Color vision restrictions for medical school admission: a discussion on regulations in ASEAN countries compared to countries across the world. International Journal of Retina and Vitreous. 2023;9:5.
37. Fanlo Zarazaga A, Gutierrez Vasquez J, Pueyo Royo V. Review of the main colour vision clinical assessment tests. Arch Soc Esp Oftalmol (Engl Ed). 2019;94:25-32.
38. Melamud A, Hagstrom S, Traboulsi E. Color vision testing. Ophthalmic Genet. 2004;25:159-87.
39. Lee YY, Granger-Donetti B, Chang C, Alvarez TL. Sustained convergence induced changes in phoria and divergence dynamics. Vision Res. 2009;49:2960-72.
40. Wong SW, Ang ZH, Crowe P. Enhancing ergonomics in robotic surgery-a review. AME Surgical Journal. 2024;4:1-7.

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Review Article

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Microbiology of Postoperative Sepsis: Pharmacotherapy, Antibiotic Resistance and Associated Mortality

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ABSTRACT

Postoperative sepsis (POS) is a condition characterized by infection occurring after surgery, often caused by microbial contamination, with potential severe consequences including widespread inflammation and organ failure. This comprehensive review delves into the intricate landscape of postoperative sepsis, causative microorganisms, global incidence, mortality rates, and diverse treatment approaches across different surgical procedures. Microbial factors, ranging from contaminated instruments to the host's skin flora, can contribute to POS. The prevalence of resistant microorganisms in healthcare settings amplifies the complexity of treatment and underscores its critical impact on postoperative outcomes. Effective pharmacotherapy forms the basis of treating POS, where timely initiation of broad-spectrum antibiotics is significant. Antibiotic choices are tailored according to local resistance patterns, where drugs such as carbapenems, vancomycin, and linezolid are commonly employed for the treatment of multi drug resistant organisms. The multifactorial nature of POS, influenced by host immunity, antibiotic usage, anaesthesia types, and surgical duration, is dissected to highlight areas for targeted intervention. The review culminates in a discussion of potential avenues for research and improvement in the management of postoperative sepsis on a global scale.

KEYWORDS postoperative sepsis, surgical infections, microbial contamination, antimicrobial resistance, mortality rates, antibiotic therapy, global incidence

INTRODUCTION

Nearly 40.0% of postoperative complications are attributed to postoperative sepsis (POS). Worldwide, POS accounts for about 20.0% of all healthcare-associated diseases. POS is an infection that may be acquired within 30 days of surgery or, in case of an implant, after a year. It is common in rural hospitals due to the lack of adequate hygienic infrastructure to perform surgeries and is also prevalent in developing and developed countries. The source of infection could be from contamination of surgical equipment or from the patient's microflora. POS has multiple risk factors, including both procedural and patient-related variables, with high body mass index (BMI) being a significant concern, with obesity (BMI ≥30 kg/m²) associated with increased surgical site infections (SSI) due to poor wound healing and immune dysregulation. Additionally, the host's immunity, use of antibiotics, the type of anaesthesia and duration of the surgery are also considerations (1). Risk factors can also be associated

with race, age, and sex of the patient as well as the proportion of untrained hospital professionals. POS is frequent after abdominal and thoracic surgery.

POS can be visualized as an infected region of the surgical site, but immune components also play a major role in this process (2). Neutrophil and monocyte activation coincides with the incidence of POS. Monocyte activation impairment may lead to defective antigen presenting ability of the cells, eventually leading to POS. Immunosuppression resulting from postoperative anergy is the major concern among causes of POS (3).

Pharmacotherapy can help prevent and manage POS, covering both prophylactic and therapeutic aspects. Antibiotics administered prior to surgery as part of preoperative antibiotic prophylaxis, can lower the risk of postoperative infections (4). Research indicates that administering antibiotics preoperatively can lower the incidence of wound infection by more than 80.0% when compared to patients who do not receive prophylactic treatment. This is especially crucial for procedures involving bone grafting, artificial implants, major dissections, or significant blood loss. Preoperative systemic prophylactic antibiotics should be administered at least half an hour before the skin incision. A number of considerations, including cost, safety, convenience of administration, pharmacokinetic profile, and bactericidal activity, are taken into consideration in choosing antibiotics. For surgical prophylaxis, cefazolin is often prescribed for individuals who have never experienced Methicillin-Resistant *Staphylococcus aureus* (MRSA) infection or β-lactam allergy. Patients with severe cefazolin allergies are frequently medicated with substitutes such as clindamycin or vancomycin. For individuals who need more defence against microbes, other antibiotics including cefazolin plus metronidazole, cefoxitin, or ertapenem may be required (5). Significant therapy with agents like carbapenems, are effective against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, and vancomycin or linezolid for early intervention are very important. Further targeted therapy with antimicrobial agents can be guided by susceptibility testing, making the determination of the intervention more precise, e.g., combining regimens of ceftriaxone with metronidazole for polymicrobial infections (6).

Microorganisms that cause POS are numerous and difficult to control as all of them are resistant to a wide range of antibiotics. The fact that microorganisms that cause POS are widespread in hospital settings is an underlying cause of their antimicrobial resistance. For this reason, the microorganisms must be widely known and development of further understanding of their specific resistance is warranted to help fight against POS. The global incidence of POS associated with different surgical conditions, is depicted in Figure 1.

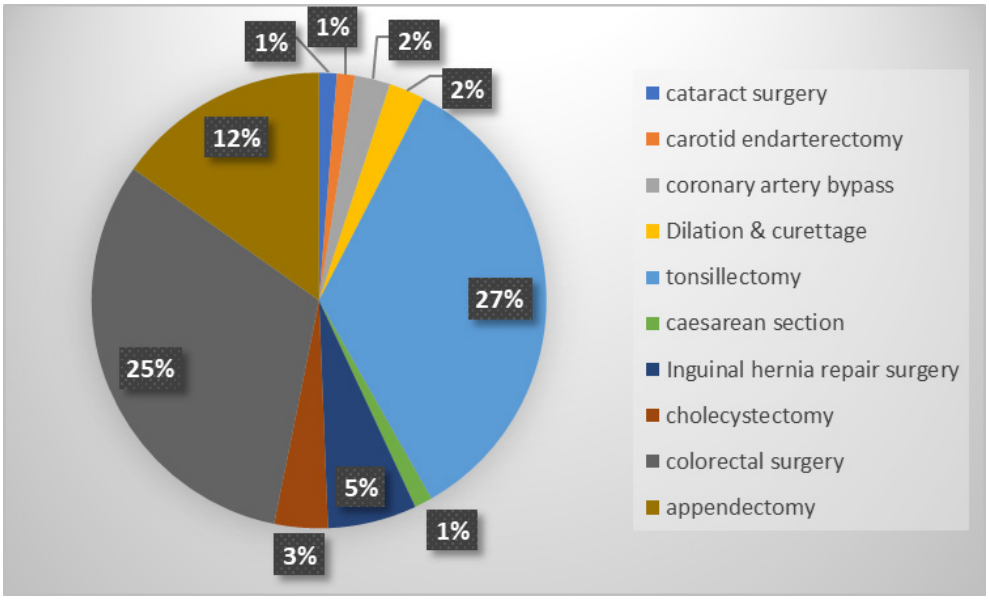

Figure 1. Global occurence of POS associated with the surgical conditions studied

CATARACT SURGERY

Cataract surgery is a common procedure in which a cataract (opaque) lens is extracted in order to restore vision by replacement with a new artificial lens. The indications for cataract surgery include obscured vision, double vision, impaired night vision, hypersensitivity to the glare of the sun and increased size of the cataract as diagnosed by clinician. An atypical yet severe post-operative septic condition subsequent to this surgical intervention is endophthalmitis (7). This condition is represented by purulent discharge because of infection but has a surprisingly low mortality rate (8).

A number of co-morbid factors have been identified that could potentially increase the risk and occurrence of post-cataract endophthalmitis. Preoperative risk factors include age ≥85 years, diabetes mellitus, immunosuppression and the use of contact lenses in addition to co-existing ophthalmic conditions like uveitis, retinal detachment, ocular prosthesis, blockage of lacrimal duct, blepharitis, canaliculitis, glaucoma, conjunctivitis and several other eye abnormalities (8).

Certain surgical incisions, such as clear corneal incision and scleral tunnel incision, are employed for cataract surgery of which the former is associated with an increased risk for the manifestation of endophthalmitis. A frequent complication in this surgery is the risk of rupture of the posterior lens capsule which can pave the way for this septic condition. Furthermore, the material of the artificial lens used for the replacement following removal of a cataract influences likelihood of acquiring sepsis. For instance, a lens made of silicon optics enhances the chances for sepsis in contrast to a lens made of acrylic optics (9).

Sepsis resulting from a galactosaemic cataract is typically triggered by bacterial infections including *E. coli*, *Klebsiella* spp., *Enterobacter* spp., Beta *Streptococcus* spp. and *Streptococcus faecalis* (10). On the other hand, MRSA (11), *Stenotrophomonas maltophilia*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Candida albicans*, *Corynebacterium* spp. (8), *Pseudomonas aeruginosa* (9) and *Propionibacterium acnes* (12) are predominantly responsible for endophthalmitis with coagulase-negative *Streptococci* accounting for the majority of cases (70.0%).

Pharmacotherapy for post-cataract septic conditions varies with respect to antibiotic sensitivity of the bacterial strains and grouping of sepsis. *E. coli*-induced sepsis in galactosaemic cataracts is treated with Cefotaxime, Ceftriaxone, piperacillin, gentamycin, ampicillin and amikacin (10). In general, Cefuroxime (9) is commonly prescribed for reducing the possibility of post-cataract endophthalmitis. Gentamycin and Vancomycin (11) are administered for endophthalmitis caused by MRSA owing to the resistance exhibited by certain strains of MRSA to Fluoroquinolones (12).

Drug resistant strains are targeted by suitable and specific antibiotics. For example: (i) a combination of Cefotaxime (inhibition of penicillin-binding proteins causing cell death) and Mecillinam (inhibition of penicillin-binding protein) (2) for multidrug resistant *E. coli* strains (13), (ii) Doripenem (inhibition of penicillin-binding proteins causing cell death) and Ceftobiprole to treat *P. aeruginosa* infections and (iii) Levonadifloxacin WCK 771 (specific binding to DNA gyrase thus terminating DNA replication) (14) to treat Fluoroquinolone resistant MRSA have demonstrated promising results.

CAROTID ENDARTERECTOMY

Carotid endarterectomy (CEA) is a surgical procedure that involves the removal of plaque from the carotid arteries in order to minimize the risk of stroke arising from carotid artery stenosis. This surgery is indicated in symptomatic cases presenting with stroke or transient ischemic attack (TIA) as well as in asymptomatic cases (15). A study reported a very low incidence of POS, about <1%, following CEA (16).

Risk factors for CEA include age ≥80 years, congestive cardiac failure (CCF), coronary artery disease (CAD), need for open heart surgery, angina pectoris, recent heart attack, chronic obstructive pulmonary disease (COPD), renal disease and prior radical neck surgery or radiation therapy.

The causative organisms responsible for POS encompass MRSA, *S. epidermidis*, *S. aureus*, *Enterobacter aerogenes*, methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Streptococcus agalactiae*, *Bacteroides fragilis*, *Streptococcus viridans*, *Proteus mirabilis*, *P. aeruginosa* (15-18)

Staphylococcus hominis and *Streptococcus pyogenes*. Pharmacotherapy for post-op CEA sepsis is crucial for successful recovery of affected people. Vancomycin and cefazolin (inhibition of cell wall synthesis) have been prescribed for preoperative antibiotic regimens (18). MRSA infection is treated with cefuroxime (inhibition of cell wall synthesis) and vancomycin, linezolid (inhibition of protein synthesis) (17). Rocephin (inhibition of cell wall synthesis) is administered for MSSA, *S. agalactiae* and *E. aerogenes* infections. Doxycycline (inhibition of protein synthesis), a broad-spectrum antibiotic, is employed for MRSE infection. Zosyn is recommended for *S. hominis* infection. Other suggested antibiotics include levofloxacin, trovafloxacin, amoxycillin/clavulanate (β-lactamase inhibition), ceftriaxone, ceftazidime and oxacillin (18). Specific strains of *S. hominis* have exhibited multidrug resistance towards penicillin, oxacillin, methicillin, kanamycin, gentamycin, streptomycin, tetracycline, erythromycin, clindamycin, chloramphenicol, cotrimoxazole and ciprofloxacin (inhibition of cell wall synthesis) for which limited alternatives exist (19).

CORONARY ARTERY BYPASS

Coronary artery bypass (CAB) is a medical procedure that re-establishes blood circulation to the heart by removing any obstruction in the coronary artery, which plays a vital role in supplying blood to heart. Reasons that demand the surgery include angina, prominent left main coronary artery stenosis, left main equivalent disease, triple vessel disease, double coronary vessel disease, stenosis involving single or multiple vessels, disabling angina, abnormal left ventricular activity, unsuccessful percutaneous transluminal coronary angioplasty (PTCA), as well as immediately after myocardial infarction (MI), arrhythmias and occlusion of grafts from previous CABs.

Postoperative septic manifestation has been recognised as a perpetuating factor contributing to increased mortality. Some of the co-morbid factors for the POS following CAB include the age factor (generally above 80 years), poor pre-operative functional management (20), chronic diseases like diabetes mellitus, congestive heart failure, chronic kidney disease, obesity (high BMI ≥30 kg/m^2), smoking (21), ill health, malnutrition, immunosuppressive effects of extracorporeal bypass, prolonged intubation and use of indwelling appliances (drains) (22). Other considerations could include infections such as pneumonia, mediastinitis, urinary tract infections, endocarditis or infected prosthetic materials, airway colonization with nosocomial bacteria (23), systemic arterial hypertension, dyslipidaemia, family history of CAD, haemodialysis and cardiogenic shock in the pre-operative period and treatment with immunosuppressive agents as in the case of an extracorporeal bypass (24).

A wide variety of microorganisms were found to be involved in sepsis development. Lineaweaver et al. (1992) observed *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. Ford et al. (1991) reported *Haemophilus* spp. and *Candida spp*. De Oliveira et al. (2010) isolated *P. mirabilis*, *S. maltophilia*, *E. aerogenes*, *S. aureus*, *Enterobacter cloacae*, *Acinetobacter calcoaceticus*, *Candida glabrata*, *S. maltophilia*, *S. viridans*, *Staphylococcus coagulase*, Flavobacterium, *S. faecalis*, *Neisseria* spp. and yeast. *S. epidermidis* and *C. albicans* were identified as the two common pathogens in various works including those of De Oliveira et al. (2010) and Michalopoulos et al. (2003). Ceftriaxone, meropenem, cefepime, teicoplanin, clindamycin and ceftazidime were the antibiotics used in those cases (20). *S. epidermidis* infection can be treated with a broad range of antibiotics including gentamycin, vancomycin, imipenem, cephapirin, clindamycin and trimethoprim-sulfamethoxazole. Pseudomonas MDR was noted to be resistant but treatable with ceftazidime, cefepime and polymyxin. Colistin (Polymyxin E), an effective drug, adheres to the lipopolysaccharides on the cell membrane, causing lysis of the cell (Table 1) (25, 26).

DILATION AND CURETTAGE

Dilation and curettage (D&C) is a gynaecological procedure which involves the dilation of the cervix and excision tissue from the uterine lining by scraping or scooping techniques using a curette. This surgery is recommended by clinicians in cases such as abnormal uterine bleeding, cervical polyps (27), vaginal bleeding, detection of cancerous cells (28), caesarean scar pregnancy (CSP) (29), molar pregnancy (30), abortion and miscarriage (31). Precipitating factors for POS include molar pregnancy, hypertension, intercourse, use of

Table 1. Drug resistance associated with postoperative sepsis

Surgery	Drug resistant microbes	Details of drug resistance	Mechanism of antibiotic resistance
Cataract surgery	Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Candida albicans*, Coagulase-negative *Staphylococci*	Penicillin, cephalosporins, carbapenems, fluoroquinolones, azoles	Altered penicillin-binding proteins (PBPs), β-lactamase production, efflux pumps, enzymatic degradation of antifungals, cell wall synthesis inhibition resistance
Carotid endarterectomy, patch angioplasty	*P. aeruginosa*, Methicillin-Resistant *Staphylococcus epidermidis* (MRSE), Methicillin-susceptible *Staphylococcus aureus* (MSSA), *Enterobacter aerogenes*, *Serratia marcescens*	Carbapenems, cephalosporins, aminoglycosides, penicillin	Efflux pump overexpression, carbapenemase enzyme production, β-lactamase production, porin loss
Coronary artery bypass	*Klebsiella pneumoniae* (ESBL-producing), Multidrug-Resistant *Pseudomonas* spp., *Enterobacter cloacae*, *Acinetobacter calcoaceticus*, *Candida glabrata*, *S. epidermidis*	Penicillin, cephalosporins, azoles, aminoglycosides	Hydrolysis of β-lactam antibiotics by ESBLs, efflux pumps, β-lactamase enzyme activity, resistance to azoles by ergosterol binding alteration, multidrug efflux pumps
Dilation & curettage	ESBL-producing *Escherichia coli*, *Streptococus agalactiae*, *Clostridium perfringens*, *Gardnerella vaginalis*, Group B Streptococcus	Cephalosporins (3rd gen), aminoglycosides, vancomycin, penicillin	Plasmid-mediated ESBL gene resistance, β-lactamase production, enzymatic inactivation of antimicrobials, altered protein binding
Tonsillectomy	Macrolide-Resistant *Streptococcus pyogenes*, *Haemophilus influenzae*, β-lactamase-producing *Bacteroides* spp.	Macrolides, penicillin, β-lactams	Methylation of 23S rRNA (blocking macrolide bind-ing), β-lactamase enzyme activity, porin modifications, altered nitro-reductase enzyme for drug activation
Caesarean section	Vancomycin-resistant *Enterococcus faecium* (VRE), *Carbapenem- Resistant E. coli*, *K. pneumoniae*, MRSA, MSSA	Vancomycin, carbapenems, penicillin, cephalosporins	VanA/VanB operons modifying D-Ala-D-Ala terminal, carbapenemase enzyme production, β-lactamase activity, altered PBPs
Inguinal hernia repair surgery	Multidrug-resistant *Acinetobacter baumannii*, Azole-Resistant *Aspergillus fumigatus*, *S. epidermidis*, *Coryne-bacterium* spp., Coagulase-negative *Staphylococci*	Azoles, β-lactams, amino-glycosides	Efflux pumps, β-lactamase enzymes, outer membrane protein loss, ergosterol binding alteration, enzymatic degradation of cell wall inhibitors
Cholecystectomy	Carbapenem-Resistant *E. coli*, *Clostridium perfringens*, *P. aeruginosa*, *Enterococcus* spp.	Carbapenems, vancomycin, aminoglycosides, cephalosporins	Carbapenemase enzyme ac-tivity, altered cell wall syn-thesis pathways, efflux pumps, β-lactamase production
Colorectal surgery	Metronidazole-resistant *Bacteroides fragilis*, ESBL-producing *E. coli*, *K. pneumoniae*, *Candida albicans*, Carbapenem-resistant *A. baumannii*	Metronidazole, carbapenems, β-lactamase, azoles	Altered nitro-reductase enzyme, hydrolysis of β-lactamase antibiotics, efflux pumps, azole resistance via ergosterol modification
Appendectomy	AmpC β-lactamase-producing *Enterobacter cloacae*, ESBL-producing *E. coli* and *Klebsiella* spp., *Enterobacter* spp., *Bacteroides fragilis*, Multi-drug-Resistant Gram-Negative Rods (GNRs)	Cephalosporins, β-lactamase, carbapenems, metronidazole	Inducible AmpC genemediated cephalosporin hydrolysis, β-lactamase enzyme production, altered nitro-reductase enzyme, efflux pumps, carbapenemase activity

tampons, douching, diabetes, cancer, alcoholism, pelvic inflammatory disease (PID), liver cirrhosis, neurological impairment (32) and placenta accreta (33).

Organisms involved in the occurrence of sepsis can cause a wide variety of manifestations ranging from fever and abdominal pain to life-threatening conditions like haemolysis, coagulopathy, uterine haemorrhage, and endocarditis. Potential pathogenic organisms cited include *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (32), *Clostridium perfringens*, *Clostridium sordelli* (34), *S. viridans*, *E. coli*, Group A *Streptococcus* (33), Group B *Streptococcus* (32), *LactoBacillus jensenii* (35), *Gardenerella vaginalis* (36) and *E. faecalis* (37).

Antibiotic therapy treatment is comprised of the combination of one or more drugs for an effective recovery. Intravenous ceftriaxone, gentamycin, doxycycline, penicillin, vancomycin (32), IV piperacillin/tazobactam, metronidazole (33, 38), cefmetazole, cefepime, cephalexin, cefuroxime, erythromycin, trimethoprim/sulfamethoxazole, ertapenem and metronidazole, ertapenem and clindamycin (33) levofloxacin and ciprofloxacin (38) are some of the suggested drugs. The mode of action of these antibiotics includes inhibition of nucleic acid synthesis and protein synthesis inhibition. In recent years, due to increased demand for these drugs employed as a remedy, several microbes have acquired resistance to antibiotics, making counter treatment a challenging task.

TONSILLECTOMY

Tonsillectomy is a surgical intervention that involves the excision of both the palatine tonsils. The common cues that indicate surgery is necessary include frequent infection instigating tonsillitis, difficulty in breathing and swallowing due to obstruction caused by swollen tonsils, obstructive sleep apnea (OSA), atypical tonsils, cancer of either/both tonsils (squamous cell carcinoma and lymphoma), haemorrhage in tonsils' blood vessels, adenoiditis, peritonsillar abscess, tonsillitis as a complication arising from immunoglobulin A nephropathy (IgAN) (39), guttate psoriasis, chronic plaque psoriasis (40), periodic fever aphthous stomatitis pharyngitis adenitis (PFAPA) syndrome (41) and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection syndrome (PANDAS) (42).

Since children represent the majority of patients referred for tonsillectomy, certain standards need to be met in order to minimize any postoperative consequences. The prime points of the paradise criteria for tonsillectomy include individuals affected at a frequency greater than or equal to seven episodes in the past year, five episodes per year for the last two years and three episodes per year for the last three years. In addition to this, vigorousness of the episodes also influences the final decision. Distributed sepsis is a quite rare phenomenon post-tonsillectomy. Young children are more susceptible to acquiring infections, tachycardia, hypotension (43), bleeding disorders (anaemia), local infection, allergic conditions and hyperthermia are among the risk factors.

Microorganisms associated with post-tonsillectomy septic infection include Aerobes – *E. coli*, Group A β Hemolytic *Streptococci* (GABHS), *Enterobacter* spp., *Haemophilus* influenza, Group C β Hemolytic *Streptococci* (GCBHS), *S. aureus*, Group F β Hemolytic *Streptococci* (GFBHS), *S. pneumoniae*, *S. viridans*, *Strep. pyogenes*; anaerobes-*Fusobacterium necrophorum* (obligate), *Bacteroides melanigenicus* gram-negative coccobacilli and gram-positive cocci. Interestingly, normal flora and unclassified *Streptococci* (44) have also been identified.

In order to reduce the possibility of developing sepsis, only a few, yet effective, antibiotics are prescribed. The administration of antibiotics reduces the intensity of infection but not the obstruction. Hence, the latter remains a primary indicator for tonsillectomy surgery. Cefazolin for the preoperative period, ampicillin and amoxicillin for *S. pyogenes* (45), amoxicillin and clavulanate potassium (Augmentin) for β-*lactamase* producing bacteria, ticarcillin disodium and clavulanate potassium (inhibition of beta lactamase) and Timentin (46) for the perioperative period have been prescribed. However, the use of antibiotics following surgery is not recommended unless it is necessary since evidence suggests that worsening of an already existing condition is possible, e.g., oral antibiotics might exaggerate the postoperative consequences (bleeding) (47).

CAESAREAN SECTION

Caesarean section or C-section (CS) is an obstetrical procedure wherein an incision is created in the mother's abdomen and/or uterus for parturition. This surgery may be opted for in cases of earlier CS, post term dates, cephalopelvic disproportion, labour dystocia, foetal distress, unfavourable cervix, rhesus incompatibility, failed induction, antepartum haemorrhage, oligohydramnios, placenta praevia, HIV infection, narrowed pelvis, breech presentation (48) fear of vaginal childbirth, to avoid episiotomy, older age and the number of previous abortions.

Associated factors that increase the prevalence of sepsis include gestational age, Cesarean section, mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, duration of labour, frequency of preoperative vaginal examinations and membrane ruptures prior to delivery. Other factors may include postoperative anaemia (49), obesity, use of intrauterine devices, avoidance of the use of plastic draping, re-disinfection, diabetes mellitus, gestational diabetes and chronic hypertension (50).

Microbial species that play a pivotal role in the development of sepsis include Beta Hemolytic *Streptococci*, *E. coli*, *S. aureus*, *Actinomyces neuii*, *S. epidermidis*, *Micrococcus* spp., *Bacillus* spp., *Propionibacterium* spp., group A and group B *Streptococci* (49, 51). A few more factors that can be added to the list include being coagulase negative for *Staphylococci*, *Klebsiella* spp., gram positive and negative organisms, *Candida spp.*, *Acinetobacter* spp., *P. aeruginosa*, *S. pneumoniae*, *Enterococcus* spp., *K. pneumoniae*, *Neisseria* and *C. freundii* (52).

Medications prescribed for treatment of POS include intravenous cefuroxime, first- or second-generation cephalosporins for *S. aureus*, second-generation cephalosporins for *E. coli*, ceftazidime, metronidazole, G-penicillin, erythromycin, gentamicin, penicillin and cephalexin (51). Tumuhamye et al. (2020) mentioned some other drugs such as vancomycin, ampicillin, netilmicin, tetracycline, trimethoprim/sulfamethoxazole, chloramphenicol, amoxicillin/clavulanic acid, ceftriaxone and imipenem which inhibit cell wall and protein synthesis (52).

Microbes carrying resistance to antibiotics include metronidazole-resistant *Actinomyces neuii* which can be countered with cefuroxime which possess bactericidal activity, blocking the interconnection of peptidoglycan and thus inhibiting bacterial cell wall synthesis. They also induce production of autolysins that leads to cell death. Another resistant organism is *Morganella morganii* that is insensitive to first and second-generation cephalosporin (51).

INGUINAL HERNIA REPAIR SURGERY

Hernia is a swelling that occurs in the abdominal wall that loosens and causes spillage of abdominal components into the inguinal canal which can be rectified by inguinal hernia repair (IHR) surgery. Unilateral or bilateral inguinal hernia, hindrance of day-to-day tasks and excruciating pain are some of the common indications for the surgery (53-55).

Diabetes mellitus, smoking (56), obesity, co-existing infection, altered immune response, increased age (>60 years), nutritional status, HIV status and gender (53) are significant influencing factors for POS. Certain other factors include complicated hernia repair, type of mesh used, history of prior mesh infection (56), operative contamination (57), ischemic heart disease, COPD (58), hypertension, liver or renal impairment, respiratory conditions, MI and peptic ulcer (59, 60).

Microorganisms involved in sepsis manifestation include *S. aureus*, coagulase negative *Staphylococci* (56, 57, 61), *E. faecalis*, Group G *Streptococcus*, *Anaerobic coccus*, *Corynebacterium*, *Hemolytic Streptococcus*, *Aspergillus fumigatus* (53), gram negative cocci, *S. epidermidis* and gram-negative bacteria (62, 63).

Chemotherapy advised for the treatment of a septic condition includes cefuroxime (53), vancomycin, cephalosporins, cefazolin (56), amoxicillin and clavulanic acid (57), ampicillin and sulbactam. Teicoplanin, oxacillin, nafcillin, piperacillin, penicillin g, imipenem, gentamycin, streptomycin, ceftriaxone, cefotaxime, arbekacin, oflaxacin, daptomycin, ceftobiprole and ceftaroline (62) are also commonly prescribed. Among the listed organisms, *A. fumigatus* was found to be resistant to azoles (63, 64) which can be mitigated by amphotericin B (disrupts the cell membrane) (65). The drug binds to ergosterol, a lipid component

of the cell wall, leading to perforation, oozing of intracellular contents and fungal cell death.

CHOLECYSTECTOMY

Cholecystectomy is a surgical intervention involving removal of the gall bladder. Conditions for which surgery is recommended include acute or chronic cholecystitis, pancreatitis, obstructive jaundice, gallstone disease (66) and cholelithiasis (67).

Older age, decreased preoperative albumin, prolonged operation time, female gender (68), chronic kidney disease, connective tissue disease, cirrhosis, complicated and uncomplicated diabetes, obesity, gallbladder perforation, antibiotic treatment (67) open or laparoscopic surgery (66), development of bile leakage, intra-abdominal abscess and pneumonia after laparoscopic cholecystectomy, degree of contamination (68), neoplasm, pre-operative razor shaving (67) are regarded as risk factors for SSI.

Organisms associated with postoperative infection include *E. coli*, *Klebsiella* spp., *Streptococcus* spp. (69), *S. aureus* (70), *Enterobacter* spp, *Enterococcus* spp. (68), *E. faecium*, *K. pneumonia*, *C. albicans*, *P. aeruginosa*, *M. morganii*, *P. mirabilis* (67), *C. perfringens* (71), (72) and *E. cloacae* (73).

Amoxicillin-clavulinic acid (73), gentamycin (67), ciprofloxacin + metronidazole (74) cefazolin (75-77) cefotaxime (78, 79) and cefuroxime (80, 81) are prescribed for infection. Resistance to metronidazole, ceftriaxone, imipenem, clindamycin, penicillin G, chloramphenicol (82), and vancomycin has been demonstrated in certain strains, including *Clostridium perfringens*. These infections may be effectively treated with alternatives such as amoxicillin, cephradine, fosfomycin (which inhibits nucleic acid synthesis), and Florfenicol (83). Thus, understanding the patterns of antibiotic resistance among important infections can be crucial for developing therapeutic approaches (Table 2).

COLORECTAL SURGERY

Colorectal surgery is a surgical procedure done to treat disorders arising from the rectum, colon or anus. Indications for surgery include abdominal adhesions, volvulus, ulcerative colitis, diverticulitis, colorectal cancer, Crohn's disease and familial adenomatous polyposis (FAP) (84).

Factors associated with this surgery include age, race, sex, diabetes, obesity, smoking, immunosuppression, steroid use, malnutrition, postoperative hypothermia, Hartmann's procedure, hypoalbuminemia, postoperative hypotension, BMI ≥30 kg/m² (85), chronic liver disease, metastatic neoplasm cardiovascular disease and chronic renal disease. Antibiotic prophylaxis, bowel preparation, fluid management, oxygen supply and skin disinfection also influence the occurrence.

E. coli, *E. cloacae*, *Aeromonas sobria*, *P. aeruginosa*, *K. pneumonia* (85, 86), *E. faecalis*, *M. morganii*, *E. faecium*, *Candida albicans* (87), *Acinetobacter baumanii*, *S. epidermidis*, *S. aureus* and *P. mirabilis* (88) are some of the microorganisms identified as causing SSI.

Aminoglycoside, ampicillin, metronidazole (89, 90) piperacillin-tazobactam, Amikacin, Amoxicillin-clavulanate, Ciprofloxacin, Co-trimoxazole, gentamicin, cefotaxime, nitrofurantoin, ceftazidime, carbapenems, ampicillin-sulbactam, linezolid, vancomycin (83), clindamycin, cephalosporins (89), neomycin, erythromycin, tobramycin and colistin sulphate (disrupts the cell membrane) (90, 91) are widely employed in the treatment of infection. Extended-spectrum β-lactamase (ESBL) producing pathogens are resistant to β-lactam antibiotics such as amoxicillin-clavulanate (92), but can be managed by administration of Meropenem, Imipenem and other carbapenems (93).

APPENDECTOMY

Appendectomy is a surgery that involves removal of the appendix in order to cure appendicitis (94, 95). Acute cholecystitis, simple and suppurative acute appendicitis, gangrenous and perforated acute appendicitis (96, 97) and lesion in the appendix are some of the conditions that necessitate the procedure. Co-morbidities for POS include age ≥60 years, African American race, morbid obesity, acute renal failure or dialysis, disseminated malignancy, open appendectomy (98), diabetes, greater incisional length, faecal contamination, and longer operative time (99).

Sepsis following surgery may involve one or more microorganisms such as *B. fragilis* and *E. coli* (97, 100). Beta *Streptococcus*, *S. aureus* (100), *P. aeruginosa*, and other gram-negative rods including *Enterococcus* and other anaerobes (96),

Bacteroides, *Klebsiella/Enterobacter* spp., *S. faecalis* and anaerobic *Streptococci* (100) may also play a role.

Sepsis can be prevented by administration of antibiotics. Cephalosporin, cefamandole, netilmicin, gentamicin (96), penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, chloramphenicol and erythromycin (94), sulbactam and ampicillin (sa), metronidazole and cefotaxime (101) are widely used in chemotherapy.

The prevalence and mortality rates associated with the postoperative sepsis conditions are summarised in Table 2 (102-108).

CONCLUSION

POS remains a significant challenge across various surgical conditions encompassing complications that extend beyond the immediate postoperative period. Microbial pathogens play a crucial role in the development and progression of sepsis, highlighting the importance of effective infection prevention strategies and targeted antimicrobial therapy. Pharmacotherapy plays an essential role in minimizing the load of POS, especially with increasing multidrug-resistant pathogens. Targeted therapies, including linezolid for vancomycin-resistant *E. faecium* and ceftazidime-avibactam for β–lactamase-producing organisms,

Table 2. List of surgical conditions, their prevalence and mortality rates due to postoperative sepsis (POS)

Surgery	Surgical prevalence	POS	Risk factors for POS	Mortality rate due to POS
Cataract surgery	7.75% (6.38% in males and 9.01% in females)	Postoperative endophthalmites	Older age, preexisting ocular inflammation	4.60% in duration of 30 days
Carotid endarterectomy, patch angioplasty	67.20%	Rare complication of infection	Diabetes mellitus (type 2, HbA1c ≥ 6.50%), poor surgical hygiene	3.00%
Coronary artery bypass	150,000 surgeries done annually	Airway colonisation, UTI	Prolonged ICU stay, obesity (BMI ≥ 35), diabetes (type 2, un-controlled HbA1c > 8.00%), smoking	32.00-79.00%
Dilation & curettage	30.00% in females	Uterine infection, bleeding (haemolysis)	Incomplete abortion, anaemia (Hb < 9 g/dL)	0.6 per 100,000 legally performed induced abortions
Tonsillectomy	13.60%	Pneumonia, superficial site infection and urinary tract infection	Immune suppression, inadequate postoperative care	7 per 100,000 operations
Caesarean section	10.00-15.00%	Post-caesarean section peritonitis, surgical site infection	Obesity, diabetes (Gestational or type 2), prolonged labor	Up to 3.00%
Inguinal hernia repair surgery	7.20% in males and 2.60% in females	Deep groin infection, surgical site infection (SSIs)	Poor surgical site preparation, immune suppression	4.00-5.00%
Cholecystectomy	8.36 to 13.81%	Intra-abdominal abscess and pneumonia	Older age, obesity, biliary tract infections	0.10-0.70%
Colorectal surgery	65.40%	Surgical site infection (SSIs)	Bowel perforation, malnutrition, prolonged surgery	13.00%
Appendectomy	12.00% in males and 23.10% in females	Intra-abdominal abscess	Delay in diagnosis, perforated appendix	17 of 311 patients (5.47%) with post-operative sepsis die within 30 days

which have had success, indicate the possibilities of such new approaches. Additionally, advances in diagnostic techniques, such as rapid pathogen identification and antimicrobial susceptibility testing, hold promise for optimizing treatment regimens and improving patient outcomes. Future research should focus on elucidating the complex interplay between host factors, microbial virulence, and surgical strategies in order to enhance personalized interventions aimed at reducing the complications of POS and its associated morbidity and mortality.

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The authors declare no conflicts of interest.

ADDITIONAL INFORMATION

Compliance with ethical standards

This manuscript does not contain studies involving animals or human participants.

Author contributions

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REFERENCES

1. George M, Iramiot J, Muhindo R, Olupot-Olupot P, Nanteza A. Bacterial aetiology and antibiotic susceptibility profile of post-operative sepsis among surgical patients in a tertiary hospital in rural eastern Uganda. Microbiol Res J Int. 2018;24:1–8.
2. Fried E, Weissman C, Sprung C. Postoperative sepsis. Curr Opin Crit Care. 2011;17:396–401.
3. Plaeke P, de Man JG, Coenen S, Jorens PG, de Winter BY, Hubens G. Clinical- and surgery-specific risk factors for post-operative sepsis: a systematic review and meta-analysis of over 30 million patients. Surg Today. 2020;50:427–39.
4. Nainu F, Permana AD, Djide NJN, Anjani QK, Utami RN, Rumata NR, Zhang J, Emran TB, Simal-Gandara J. Pharmaceutical approaches on antimicrobial resistance: prospects and challenges. Antibiotics (Basel). 2021;10:981. PubMed PMID 34439031.
5. Crader MF, Varacallo M. Preoperative Antibiotic Prophylaxis. [Updated 2023 Aug 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442032/
6. Bae JM. Clinical characteristics of ceftriaxone plus metronidazole in complicated intra-abdominal infection. Ann Surg Treat Res. 2015;89:43-7.
7. Freeman EE, Roy-Gagnon M, Fortin E, Gauthier D, Popescu M, Boisjoly H. Rate of endophthalmitis after cataract surgery in Quebec, Canada, 1996-2005. Arch Ophthalmol. 2010;128:230–4.
8. Crosby N, Polkinghorne PJ, Kim B, McGhee CN, Welch S, Riley A. Mortality after endophthalmitis following contemporary phacoemulsification cataract surgery. Clin Exp Ophthalmol. 2018;46:903–7.
9. Niyadurupola N, Astbury N. Endophthalmitis: controlling infection before and after cataract surgery. Community Eye Health. 2008;21:9–10.
10. Rathi N, Rathi A. Galactosemia presenting as recurrent sepsis. J Trop Pediatr. 2011;57:487–9.
11. Deramo VA, Lai JC, Winokur J, Luchs J, Udell IJ. Visual outcome and bacterial sensitivity after methicillin-resistant *Staphylococcus aureus*-associated acute endophthalmitis. Am J Ophthalmol. 2008;145:413-417.
12. Callegan MC, Engelbert M, Parke DW, Jett BD, Gilmore MS. Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions. Clin Microbiol Rev. 2002;15:111-24.
13. Rosenkilde CEH, Munck C, Porse A, Linkevicius M, Andersson DI, Sommer MOA. Collateral sensitivity constrains resistance evolution of the CTX-M-15 β-*lactamase*. Nat Commun. 2019;10:618. PubMed PMID: 30728359
14. Rai S, Rattan V. Efficacy of feracrylum as topical hemostatic agent in therapeutically anticoagulated patients undergoing dental extraction: a comparative study. J Maxillofac Oral Surg. 2019;18:579-83.
15. Khadim M, Blair PH, McKinley A, Hood JM, Harkin DW. Successful surgical treatment of methicillin-resistant staphylococcal carotid patch infection. Eur J Vasc Endovasc Surg Extra. 2005;10:122-5.
16. Stone PA, Srivastava M, Campbell JE, Mousa AY, Hass SH, Kazmi H, et al. A 10-year experience of infection following carotid endarterectomy with patch angioplasty. J Vasc Surg. 2011;53:1473-7.
17. Murphy GJ, Pararajasingam R, Nasim A, Dennis MJ, Sayers RD. Methicillin-resistant *Staphylococcus aureus* infection in vascular surgical patients. Ann R Coll Surg Engl. 2001;83:158-63.
18. Rockman CB, Su WT, Domenig C, Lamparello PJ, Adelman MA, Jacobowitz GR, et al. Postoperative infection associated with polyester patch angioplasty after carotid endarterectomy. J Vasc Surg. 2003;38:251-6.
19. Latz CA, Boitano LT, Schwartz SI, Swerdlow NJ, Dansey K, Varkevisser RR, et al. Contemporary mor-

tality after emergent open repair of complex abdominal aortic aneurysms. J Vasc Surg. 2021;73:39-47.e1. PubMed PMID: 32361067
20. Karamnov S, Brovman EY, Greco KJ, Urman RD. Risk factors and outcomes associated with sepsis after coronary artery bypass and open heart valve surgeries. Semin Cardiothorac Vasc Anesth. 2018;22:359-68.
21. Haas JP, Evans AM, Preston KE, Larson EL. Risk factors for surgical site infection after cardiac surgery: The role of endogenous flora. Heart Lung. 2005;34:114-20.
22. Ford EG, Baisden CE, Matteson ML, Picone A. Sepsis after coronary bypass grafting: evidence for loss of the gut mucosal barrier. Ann Thorac Surg. 1991;52:514-7.
23. Lineaweaver WC, Hill MK, Buncke GM, Follansbee S, Buncke HJ, Wong RK, et al. Aeromonas hydrophila infections following use of medicinal leeches in replantation and flap surgery. Ann Plast Surg. 1992;29:238-44.
24. Oliveira DC, Oliveira Filho JB, Silva RF, Moura SS, Silva DJ, Egito ES, et al. Sepsis in the postoperative period of cardiac surgery: problem description. Arq Bras Cardiol. 2010;94:332-6.
25. Michalopoulos A, Sparos L. Post-operative wound infections. Nurs Stand. 2003;17:53-6.
26. Benito N, Mur I, Ribera A, Soriano A, Rodriguez-Pardo D, Sorli L, et al.; REIPI (Spanish Network for Research in Infectious Disease) Group for the Study of Prosthetic Joint Infections/GEIO (Group for the Study of Osteoarticular Infections), SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology). The different microbial etiology of prosthetic joint infections according to route of acquisition and time after prosthesis implantation, including the role of multidrug-resistant organisms. J Clin Med. 2019;8:673.
27. Cormio G, Bettocchi S, Ceci O, Nappi L, Di Fazio F, Cacciapuoti C, Selvaggi L. Antimicrobial prophylaxis in laparoscopic gynecologic surgery: a prospective randomized study comparing amoxicillin-clavulanic acid with cefazolin. J Chemother. 2003;15:574-8.
28. Coleman DV, Mackenzie EF, Gardner SD, Poulding JM, Amer B, Russell WJ. Human polyomavirus (BK) infection and ureteric stenosis in renal allograft recipients. J Clin Pathol. 1978;31:338-47.
29. Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, et al. The epidemiology of sepsis in Chinese ICUs: a national cross-sectional survey. Crit Care Med. 2020;48:e209-18.
30. Piscitelli P, Iolascon G, Innocenti M, Civinini R, Rubinacci A, Muratore M, et al. Painful prosthesis: approaching the patient with persistent pain following total hip and knee arthroplasty. Clin Cases Miner Bone Metab. 2013;10:97-110.
31. Roche NA, Vermeersch HF, Stillaert FB, Peters KT, De Cubber J, Van Lierde K, et al. Complex facial reconstruction by vascularized composite allotransplantation: The first Belgian case. J Plast Reconstr Aesthet Surg. 2015;68:362-71.
32. McKenna PB, O'Shea K, Masterson EL. Two-stage revision of infected hip arthroplasty using a shortened post-operative course of antibiotics. Arch Orthop Trauma Surg. 2009;129:489-94.
33. Wang H, Liu B, Tang Y, Chang P, Yao L, Huang B, et al. Improvement of Sepsis Prognosis by Ulinastatin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2019;10:1370. PubMed PMID: 31849646
34. Yansouni CP, Dendukuri N, Liu G, Fernandez M, Frenette C, Paraskevas S, Sheppard DC. Positive cultures of organ preservation fluid predict postoperative infections in solid organ transplantation recipients. Infect Control Hosp Epidemiol. 2012;33:672-80.
35. Alamo JM, Barrera L, Marín LM, Bernal C, Suarez G, Serrano J, et al. Results of liver transplantation with donors older than 70 years: a case-control study. Transplant Proc. 2011;43:2227-9.
36. McCool RA, DeDonato DM. Bacteremia of *Gardnerella vaginalis* after endometrial ablation. Arch Gynecol Obstet. 2012;286:1337-8.
37. Tymon-Rosario J, Chuang M. Selective reduction of a heterotopic cesarean scar pregnancy complicated by septic abortion. Case Rep Obstet Gynecol. 2018;2018:6478589. PubMed PMID: 30420929
38. Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. Am J Cardiol. 2007;100:1702-8.
39. Sethi S, Zand L, Nasr SH, Glassock RJ, Fervenza FC. Focal and segmental glomerulosclerosis: Clinical and kidney biopsy correlations. Clin Kidney J. 2014;7:531-7.
40. Wu W, Debbaneh M, Moslehi H, Koo J, Liao W. Tonsillectomy as a treatment for psoriasis: a review. J Dermatolog Treat. 2014;25:482-6.
41. Sumilo D, Nirantharakumar K, Willis BH, Rudge GM, Martin J, Gokhale K, et al. Long term impact of prophylactic antibiotic use before incision versus after cord clamping on children born by caesarean section: Longitudinal study of UK electronic health records. BMJ Clin Res. 2022;377:e069704. PubMed PMID: 35580876
42. Wilson SK, Mora-Estaves C, Egydio P, Ralph D, Habous M, Love C, et al. Glans necrosis following penile prosthesis implantation: prevention and treatment suggestions. Urology. 2017;107:144-8.
43. Patil R, Kurdi M. Sepsis: An unusual post-tonsillectomy complication. Indian J Clin Anaesth. 2018;5:459-60.
44. Yildirim I, Okur E, Ciragil P, Aral M, Kilic MA, Gul M. Bacteraemia during tonsillectomy. J Laryngol Otol. 2003;117:619-23.
45. Piltcher OB, Scarton FB. Antibiotic use in tonsillectomies: Therapeutic or prophylactic? Required or excessive? Rev Bras Otorrinolaringol. 2005;71:686-90.
46. Grandis JR, Johnson JT, Vickers RM, Yu VL, Wagener MM, Wagner RL, et al. The efficacy of perioperative antibiotic therapy on recovery following tonsillectomy in adults: Randomized double-blind placebo-controlled trial. Otolaryngol Head Neck Surg. 1992;106:137-42.
47. Aljfout Q, Alississ A, Rashdan H, Maita A, Saraireh M. Antibiotics for post-tonsillectomy morbidity: comparative analysis of a single institutional experience. J Clin Med Res. 2016;8:385-8
48. Lavender R, Mythen M, Bao J, Chapman RH, Michard F. Impact of postsurgical complications on hospital costs and margins. Crit Care. 2015;19:1-201.

49. Hawrylyshyn PA, Bernstein P, Papsin FR. Risk factors associated with infection following cesarean section. Am J Obstet Gynecol. 1981;139:294-8.
50. Pelle H, Jepsen OB, Larsen SO, Bo J, Christensen F, Dreisler A, et al. Wound infection after cesarean section. Infect Control Hosp Epidemiol. 1986;7:456-61.
51. Nuutila K, Katayama S, Vuola J, Kankuri E. Human wound-healing research: Issues and perspectives for studies using wide-scale analytic platforms. Adv Wound Care (New Rochelle). 2014;3:264-71.
52. Tumuhamye J, Sommerfelt H, Bwanga F, Ndeezi G, Mukunya D, Napyo A, et al. Neonatal sepsis at Mulago national referral hospital in Uganda: etiology, antimicrobial resistance, associated factors and case fatality risk. PLoS One. 2020;15:e0237085. PubMed PMID: 32776958.
53. Aufenacker TJ, van Geldere D, Van Mesdag T, Bossers AN, Dekker B, Scheijde E, et al. The role of antibiotic prophylaxis in prevention of wound infection after Lichtenstein open mesh repair of primary inguinal hernia: A multicenter double-blind randomized controlled trial. Ann Surg. 2004;240:955-61.
54. Wałęga P, Scheyer M, Kenig J, Herman RM, Arnold S, Nowak M, Cegielny T. Two-center experience in the treatment of hemorrhoidal disease using Doppler-guided hemorrhoidal artery ligation: functional results after 1-year follow-up. Surg Endosc. 2008;22: 2379-83.
55. Nieuwenhuizen J, Halm JA, Jeekel J, Lange JF. Natural course of incisional hernia and indications for repair. Scand J Surg. 2007;96:293-6.
56. Harth KC, Rosen MJ, Thatiparti TR, Jacobs MR, Halaweish I, Bajaksouzian S, et al. Antibiotic-releasing mesh coating to reduce prosthetic sepsis: an in vivo study. J Surg Res. 2010;163:337-43.
57. Delikoukos S, Tzovaras G, Liakou P, Mantzos F, Hatzitheofilou C. Late-onset deep mesh infection after inguinal hernia repair. Hernia. 2007;11:15-7.
58. Dai W, Chen Z, Zuo J, Tan J, Tan M, Yuan Y. Risk factors of postoperative complications after emergency repair of incarcerated groin hernia for adult patients: A retrospective cohort study. Hernia. 2019;23:267-76.
59. Mbah N. Morbidity and mortality associated with inguinal hernia in Northwestern Nigeria. West Afr J Med. 2007;26:288-92.
60. Ou L, Chen J, Hillman K, Flabouris A, Parr M, Assareh H, Bellomo R. The impact of post-operative sepsis on mortality after hospital discharge among elective surgical patients: a population-based cohort study. Crit Care. 2017;21:1-13.
61. Flament JB, Palot JP, Fitzgibbons Jr R, Greenburg AG. Prosthetic repair of massive abdominal ventral hernias. In: Nyhus and Condon's Hernia. 5th ed. Philadelphia:Lippincott Williams and Wilkins; 2002. p. 341-66.
62. Kristich CJ, Djorić D, Little JL. Genetic basis for vancomycin-enhanced cephalosporin susceptibility in vancomycin-resistant enterococci revealed using counterselection with dominant-negative thymidylate synthase. Antimicrob Agents Chemother. 2014;58:1556-64.
63. Perl TM. Impact on outcome of premorbid and morbid functional status among patients with bloodstream infections [Thesis]. Montreal: McGill University. 1994.
64. Hata DJ, Humphries R, Lockhart SR, College of American Pathologists Microbiology Committee. Candida auris: An emerging yeast pathogen posing distinct challenges for laboratory. Arch Pathol Lab Med. 2020;144:107-14
65. Calvo B, Melo AS, Perozo-Mena A, Hernandez M, Francisco EC, Hagen F, et al. First report of Candida auris in America: Clinical and microbiological aspects of 18 episodes of candidemia. J Infect. 2016;73:369-74.
66. Jaafar G, Hammarqvist F, Enochsson L, Sandblom G. Patient-related risk factors for postoperative infection after cholecystectomy. World J Surg. 2017;41: 2240-4.
67. Sánchez-Santana T, del-Moral-Luque JA, Gil-Yonte P, Bañuelos-Andrío L, Durán-Poveda M, Rodríguez-Caravaca G. Efecto de la adecuación a protocolo de la profilaxis antibiótica en la incidencia de infección quirúrgica en apendicectomías. Estudio de cohortes prospectivo. Cir Cir. 2017;85:208-13. [in Spanish]
68. Saud JD, Al-Hail MC. Surgical site infections after laparoscopic cholecystectomy. Basrah J Surg. 2010;16:119-21.
69. Den Hoed PT, Boelhouwer RU, Veen HF, Hop WCJ, Bruining HA. Infections and bacteriological data after laparoscopic and open gallbladder surgery. J Hosp Infect. 1998;39:27-37.
70. Yanni F, Mekhail P, Morris-Stiff G. A selective antibiotic prophylaxis policy for laparoscopic cholecystectomy is effective in minimizing infective complications. Ann R Coll Surg Engl. 2013;95:345-7.
71. Tansuphasiri U, Deepradit S, Phulsuksombati D, Tangkanakul W. A test strip IgM dot-ELISA assay using leptospiral antigen of endemic strains for serodiagnosis of acute leptospirosis. J Med Assoc Thai. 2005;88:391-8.
72. Ch'ng JK, Ng SY, Goh BK. An unusual cause of sepsis after laparoscopic cholecystectomy. Gastroenterology. 2012;143:e1-2. PubMed PMID: 23089543.
73. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: A randomized clinical trial. JAMA. 2014;312:145-54.
74. Yildiz B, Abbasoglu O, Tirnaksiz B, Hamaloglu E, Ozdemir A, Sayek I. Determinants of postoperative infection after laparoscopic cholecystectomy. Hepatogastroenterology. 2009;56:589-92.
75. Kusaba T. Safety and efficacy of cefazolin sodium in the management of bacterial infection and in surgical prophylaxis. Clin Med Ther. 2009;1:CMT-S2096.
76. Chang JM, Lee HJ, Goo JM, Lee HY, Lee JJ, Chung JK, et al. False positive and false negative FDG-PET scans in various thoracic diseases. Korean J Radiol. 2006;7:57-69.
77. Matsui Y, Satoi S, Kaibori M, Toyokawa H, Yanagimoto H, Matsui K, et al. Antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized controlled trial. PLoS One. 2014;9:e106702. PubMed PMID: 25192389
78. Tocchi A, Lepre L, Costa G, Liotta G, Mazzoni G, Maggiolini F. The need for antibiotic prophylaxis in elective laparoscopic cholecystectomy: A prospective randomized study. Arch Surg. 2000;135:67-70.
79. Pacifici GM. Clinical pharmacology of tigecycline in children. Ann Clin Pharmacol Toxicol. 2021;2:33-8.
80. Naqvi MA, Mehraj A, Ejaz R, Mian A. Role of prophylactic antibiotics in low risk elective laparoscopic

cholecystectomy: Is there a need? J Ayub Med Coll Abbottabad. 2013;25:172-4.
81. Thønnings S, Jansåker F, Gradel KO, Styrishave B, Knudsen JD. Cefuroxime compared to piperacillin/tazobactam as empirical treatment of *Escherichia coli* bacteremia in a low Extended-spectrum beta-lactamase (ESBL) prevalence cohort. Infect Drug Resist. 2019;12:1257-64.
82. Akhi MT, Ghotaslou R, Beheshtirouy S, Asgharzadeh M, Pirzadeh T, Asghari B, et al. Antibiotic susceptibility pattern of aerobic and anaerobic bacteria isolated from surgical site infection of hospitalized patients. Jundishapur J Microbiol. 2015;8:e20309. PubMed PMID: 26421133
83. Ali M, Usman M, Khan Z, Khan KM, Hussain R, Khanzada K. Endoscopic third ventriculostomy for obstructive hydrocephalus. J Coll Physicians Surg Pak. 2013;23:338-41.
84. Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. Patient Saf Surg. 2010;4:5. PubMed PMID: 20338045.
85. Anannamcharoen S, Vachirasrisirikul S, Boonya-Assadorn C. Incisional surgical site infection in colorectal surgery patients. J Med Assoc Thai. 2012;95:42-7.
86. Lu X, Aoun E, Gaidos JK, Bickston SJ. Complications of acute pancreatitis. Pract Gastroenterol. 2012;10:1-19.
87. Pochhammer J, Köhler J, Schäffer M. Colorectal surgical site infections and their causative pathogens: Differences between left-and right-side resections. Surg Infect (Larchmt). 2019;20:62-70.
88. Zhang X, Wang Z, Chen J, Wang P, Luo S, Xu X, et al. Incidence and risk factors of surgical site infection following colorectal surgery in China: A national cross-sectional study. BMC Infect Dis. 2020;20:837. PubMed PMID: 33183253
89. Colizza S, Rossi S. Antibiotic prophylaxis and treatment of surgical abdominal sepsis. J Chemother. 2001;13(Supplement_4):193-201.
90. Mulder T, Kluytmans-van den Bergh M, Vlaminckx B, Roos D, de Smet AM, de Vos tot Nederveen Cappel R, et al. Prevention of severe infectious complications after colorectal surgery using oral non-absorbable antimicrobial prophylaxis: Results of a multicenter randomized placebo-controlled clinical trial. Antimicrob Resist Infect Control. 2020;9:84. PubMed PMID: 32539786
91. Mihaljević L, Mihaljević S, Vasilj I, Čavaljuga S, Serdarević F, Soldo I. Empirical antibiotic therapy of sepsis in surgical intensive care unit. Bosn J Basic Med Sci. 2007;7:266-70.
92. Simillis C, Kalakouti E, Afxentiou T, Kontovounisios C, Smith JJ, Cunningham D, et al. Primary tumor resection in patients with incurable localized or metastatic colorectal cancer: a systematic review and meta-analysis. World J Surg. 2019;43:1829-40.
93. Gutiérrez A, Rivero M, Martín-Arranz MD, García Sánchez V, Castro M, Barrio J, et al. Perioperative management and early complications after intestinal resection with ileocolonic anastomosis in Crohn's disease: Analysis from the PRACTICROHN study. Gastroenterol Rep (Oxf). 2019;7:168-75.
94. Barnes BA, Behringer GE, Wheelock FC, Wilkins EW. Treatment of appendicitis at the Massachusetts General Hospital (1937-1959). JAMA. 1962;180:122-6.
95. Blomqvist PG, Andersson RE, Granath F, Lambe MP, Ekbom AR. Mortality after appendectomy in Sweden, 1987–1996. Ann Surg. 2001;233:455-60.
96. Stone HH, Haney BB, Kolb LD, Geheber CE, Hooper CA. Prophylactic and preventive antibiotic therapy: Timing, duration and economics. Ann Surg. 1979;189:691-9.
97. Gottrup F, Hunt TK. Antimicrobial prophylaxis in appendectomy patients. World J Surg. 1982;6:306-11.
98. Ninh A, Wood K, Bui AH, Leitman IM. Risk factors and outcomes for sepsis after appendectomy in adults. Surg Infect (Larchmt). 2019;20:601-6.
99. Noorit P, Siribumrungwong B, Thakkinstian A. Clinical prediction score for superficial surgical site infection after appendectomy in adults with complicated appendicitis. World J Emerg Surg. 2018;13:23. PubMed PMID: 29946346
100. Parthiban N, Harish M. A study on microbiology culture of acute appendicectomy specimen and its correlation with wound infection. Int Surg J. 2017;4:2212-5.
101. Foster MC, Morris DL, Legan C, Kapila L, Slack RCB. Perioperative prophylaxis with sulbactam and ampicillin compared with metronidazole and cefotaxime in the prevention of wound infection in children undergoing appendectomy. J Pediatr Surg. 1987;22:869-72.
102. Tseng VL, Chlebowski RT, Yu F, Cauley JA, Li W, Thomas F, et al. Association of cataract surgery with mortality in older women: Findings from the Women's Health Initiative. JAMA Ophthalmol. 2018;136:3–10.
103. Bennett KM, Scarborough JE, Shortell CK. Predictors of 30-day postoperative stroke or death after carotid endarterectomy using the 2012 carotid endarterectomy-targeted American College of Surgeons National Surgical Quality Improvement Program database. J Vasc Surg. 2015;61:103–11.
104. Cooper DB, Menefee GW. Dilation and curettage. InStatPearls: StatPearls Publishing. [Internet]. 2023 May [cited 2024 Jun]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK568791/
105. Edmonson MB, Zhao Q, Francis DO, Kelly MM, Sklansky DJ, Shadman KA, Coller RJ. Association of patient characteristics with postoperative mortality in children undergoing tonsillectomy in 5 US states. JAMA. 2022;327:2317–25.
106. O'Brien WJ, Gupta K, Itani KMF. Association of postoperative infection with risk of long-term infection and mortality. JAMA Surg. 2020;155:61–8.
107. Lebeau R, Traoré M, Anzoua KI, Kalou IL, N'Dri AB, Aguia B, et al. Prognostic factors of postoperative morbidity and mortality of adult strangulated groin hernia. Indian J Surg. 2016;78:192–6.
108. Sandblom G, Videhult P, Crona Guterstam Y, Svenner A, Sadr-Azodi O. Mortality after a cholecystectomy: A population-based study. HPB (Oxford). 2015;17:239-43.

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Review Article

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A Narrative Review of the Understanding of Post-operative Wound Care in Ayurveda Literature

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ABSTRACT

The intricacies of meticulous wound healing or *Vrana Ropana* has been comprehensively reviewed and diligent attempts have been made at understanding the mechanisms involved in optimal wound healing via the comprehensive explanations of both Ayurveda and contemporary literature to achieve a much sought after integration of post-surgical wound care. Post-operative wound care protocols are regularly and rigorously updated as the burdens of post-surgical wound complications are on the rise. A thorough understanding of surgical wounds, stages of wound healing and optimal wound care along with identifying red flags indicating susceptibility to complications. Classic Ayurveda documents describe specialised wound care strategies associated with the use of surgical instruments as well as para-surgical therapy related to therapeutic cautery, caustic cauterization as well as wounds caused by leeches in blood-letting therapies. This presents an opportunity for the integration of those strategies with conventional knowledge in present-day surgical care which could potentially increase the efficacy and precision of wound care by minimising post-operative complications. Databases like PubMed and Scopus were searched using keywords including Sadyo *Vrana*, *Vrana Ropana*, Sastra Karma, post-operative wound care, post-surgical care and Ayurvedic methods for preventing surgical site infections. Comparison of types of wounds, mechanisms of healing and post-operative care according to evidence-based Ayurveda principles with relevant contemporary literature potentially increase understanding of what is required for a holistically integrated care plan which can help achieve uneventful post-operative surgical wound healing. To that end, it is necessary both to understand the conventional care of surgical wounds and to compare that with the existing care of post-surgical wounds as well as to identify new scopes of care including highlighting areas of bridging integrative approaches to reduce post-operative complications and to attain optimum wound healing.

KEYWORDS *Vrana*, post-operative wound healing, *Sastra Karma*

INTRODUCTION

Post-operative wound care attracts particular attention and exhaustive research interest as it is one of the significant burdens of the health care industry because it can result in undue burden on the health care economy. Achieving an uneventful postoperative wound healing process can be an arduous process which helps determine both surgical outcomes as well as impacts on the expected quality of life. Successful post-operative

care is the result of a harmonious intervention which minimizes microbial colonization and includes both proper diets and lifestyle interventions. The pivotal function of the physiological process of wound healing can be greatly facilitated by minimizing risks of infections and enabling active wound healing through the integration of successful wound care practices. The importance of identifying optimal care for wound healing is higlighted in references which state that patients with post-operative complications can be seriously affected by consequences such as unfavourable psychosocial (1) and functional outcomes which can also increase financial burdens by prolonging the period of hospitalisation (2). Various studies have suggested that there can be up to a six-fold increase of hospitalization costs for patients with surgical site infections (SSI) with the amount depending on the surgery done, the health care setting chosen and the type of infection (3-5). Infections can also account for an increase of up to 6.0% in unplanned readmissions (6) That is particularly disturbing because post-operative complications, including SSIs, are usually preventable. Many medical professionals assert that facilitating patient participation in self-management of wound care practices can help reduce the incidence of these complications (7).

Ayurveda, an ancient Indian traditional system that has withstood the test of time, has its own unique concepts when it comes to the care of wounded individuals. Regarding morbidity from wounds worldwide, it has been reported that of every million patients around 10,000 will die due to microbial infections (8). Studies have also revealed that one in four surgical wounds develops complications within the first 14 days of the post-operative period (9).

Acharya Sushruta, who is known as the Father of Surgery, has stated that care of wounds requires a multifarious approach. References can be found in the initial chapters of his *Comrstpendium Susruta Samhita*, continuing through to almost the final *sthanas*. This is evidence that Acharya *Susruta* gives importance to *vrana* (wounds) and defines wounds as something which results in the disruption of *shareeradhatu* (body tissues), leaves *vranavastu* (scars) after *ropana* (healing) which remain till the end of life. He describes the classification of *vrana*, *sadya-asadyata* (prognosis) and its management in detail, emphasizing the importance of wound care (10). Studies across the world have revealed that the overall pooled incidence of surgical site infection is 2.5% and that it varies among the WHO regions of the world (11).

The aim of the present review is to explore the types of post-operative wounds in Ayurveda following employment of various surgical modalities such as Shastra Karma (surgical procedures) and Anusastra Karma (para surgical procedures). The objective is to identify protocols that could be integrated to achieve more comprehensive wound management.

METHODS

A comprehensive literary search of the compendium of *Sushruta Samhita* was carried out to identify the steps undertaken in treatment of post-operative wounds. Various clinical conditions which have resulted could potentially result. In substantial contributions to wound healing and reducing infections were identified. An extensive review of published research papers and attempts at correlating them with contemporary research on factors contributing to wound healing was conducted. Various databases, e.g., PubMed and Scopus, were included using keywords like post-operative wound, SSI, *Vrana Ropana*, Sady-*ovrana* and filters like clinical trials, systematic review within five years and free full text.

REVIEW OF LITERATURE

Contemporary classification of surgical wounds

The currently most widely accepted surgical wound classification was initially developed in 1964 by the National Academy of Sciences and the National Research Council with the aim of representing the bacterial load in a surgical field. The Centre for Disease Control and Prevention (CDC) later refined this system by establishing four different classes of wound status as outlined below (12).

- Class 1 wounds - Clean wounds are aptly called so due to the lack of infection, to not exhibiting inflammatory signs and being closed. Examples of clean wounds include an inguinal hernia repair, a thyroidectomy and a mastectomy.

• Class 2 wounds - Clean-contaminated wounds may have a low level of contamination and may involve entry into the respiratory, alimentary, genital, or urinary tracts but only under controlled circumstances.

• Class 3 wounds – Contaminated wounds typically result from a breach in sterile techniques or leakage from the gastrointestinal tract. Incisions resulting from acute or non-purulent inflammation are also considered Class 3 wounds.

• Class 4 wounds – Dirty or infected wounds can result from inadequate treatment of traumatic wounds, gross purulence, and evident infections. When tissues lose vitality, it can lead to Class 4 wounds. These wounds are often caused by surgery or from microorganisms found in perforated organs (12).

This classification system provides a guideline regarding the susceptibility of infection of sites post-operatively, and thus help prepare the surgeon to undertake a different approach to managing them. Each class has a postoperative risk of a surgical site infection (SSI) with scores of 1% to 5.0%, 3.0% to 11.0%, 10.0% to 17.0%, and more than 27.0%, respectively (13).

Acharya Susruta, while discussing the prognosis of wounds, provides a classification based on the site upon which the wound is inflicted of the wound. Acharya classifies wounds as *sadhya*, *yaapya* and *asadhya* (14). Saadhya *vrana* (wounds which are easily healed) : Wounds located on the buttocks (*Sphik*), about the anus (*guda*), the organs of regeneration (*paayu*, *prajanan*), on the back (*prushta*), forehead (*lalaata*), cheek (*ganda*) or lips (*oshta*), and those in the region of the external ears (*karna*), on the testes (*phala kosha*), the abdomen (*udara*), in the cavity of the mouth (*mukhabhyantara*), about the nape of the neck, or above the clavicles (*jatru*) can be easily healed.

Dushchikitsya vrana (14) (wounds which are difficult to treat/heal): wounds in areas like the eyes (*akshi*), in tooth area (*danta*), the nostrils (*nasa*), the outer canthus eye (*apanga*), in the cavity of the ears (*shrotra*), the abdomen or the umbilicus(*nabhi*), or about any suture of the body (*sevani*), hips (*nitamba*), ribs (*parshwa*), abdomen (*kukshi*), chest (*vaksha*), axillary region (*kakshanta*) or the joints (*sandhi*). In addition, if the wounds are found to have exudates like frothy blood or pus with a gurgling sound, or to contain any foreign matter embedded in their inside, are healed only with the greatest difficulty. Some of the clinical scenarios like an abscess or an ulcer appearing in the nether region of the body and pointing upward, or appearing on the extremity of the scalp (*romanta*) or about the end of a finger-nail, or in any of the vulnerable parts of the body (*marma*), as well as those affecting either of the thigh bones (*femurs*), should be looked upon as equally hard to cure. Similarly, an abscess or an ulcer affecting a bone of the pelvis (*shronikanda*-acetabulum), as well as a fistula in ano opening inward should be regarded as hard to cure.

Yapya vrana (14) (requires treatment for a long duration): an ulcer incidental to, and affecting the seat of any of the following diseases, e.g., avapathika (paraphimosis), or niruddha-prakash (phimosis), or sanniruddha-*guda* (constriction of the anus), or jathara (abdominal-dropsy), or granthi (glandular inflammation), and are characterised by the germination of parasites in their interior, as well as those appearing in the cavity of the abdomen, affecting the mucous linings of the intestines, or brought about by the corrosive secretions of a *nasa*l catarrh (pratishyava), and infestations with parasites should be considered as only admitting of a palliative treatment.

Asadhya *vrana* (14) (incurable or involving a non-healing criteria): an ulcer (*vrana*) cropping up like a fleshy tumour which is painful and containing pus in its inside, and which is characterised by a copious secretion, with its edges raised like those of the genitals of a mare, should be understood as belonging to the incurable type. A condylomatous (papillomatous) ulcer which is soft and raised like the horn of a cow, or one which is moderately raised or elevated at its base and which secretes an exudation of vitiated blood or a thin slimy secretion, should be likewise regarded as incurable. An ulcer with an embossed or heaved up centre, and one dipped or fissured at its extremity should be regarded as past all remedy. An ulcer covered over with shreds of ligaments and looking as if studded with loose shreds of hemp should be given up as incurable. Similarly, an ulcer due to the deranged condition of any of the fundamental humours and secreting an exudation composed of coagulated blood, fat, marrow and brain matter should be deemed incurable. Surgical procedures of this type can result in a wound of such status, so must be judiciously handled.

Classification of wounds by Acharya *Susruta* (Ayurveda)

1. *Vranas* are broadly classified into one of two types based on their origin and etiology (15).

a. Nija*vrana* (Shareera) are caused by involvement of Doshas including combination of two or three doshas) and

b. Aganthuja*vranas* are caused by environmental or extrinsic elements including those caused by incision, punctures, lacerations, poisoned cuts, bruises etc. It can also be caused by bites of humans, animals, birds, reptiles, etc.)

2. Based on the involvement of Doshas and amount of dushti, *Vranas* are classified into either Dushta *vrana* or Shudha *vrana*. Those with considerable features of dosha dushti are called Dushta *vrana* and those with minimal to minor features of dosha dushti are called as shudha *vranas* (16).

3. *Vrana* is also classified into the *Sadyo vrana* variety which is initiated by external causes including accidental wounds, traumatic wounds and surgical wounds. They are further sub-divided into six types which are synonymously addressed as aganthuja*vranas* or sudha*vranas* (17).

a) Chinna vrana - Vrana is oblique/straight, separation of body parts.

b) Bhinna vrana - Perforation puncture of Aashayas, exuding mild Sraava

c) Vidha Vrana - Injury to any part of the body other than Aashaya or Uttundita.

d) Kshata Vrana - Vrana which is neither Ati Chinna nor Ati-Bhinna, but having features of both and being irregular in shape.

e) Pichita Vr*ana* - Flattening of any part of body along with Asthi, filled with Rakta and Majja.

f) Ghrusta V*rana* – Caused by rubbing on a rough and hard surface causing any part of the body to lose its skin. It is accompanied by watery exudation and is called ghrista *vrana* (abrasive wounds).

Understanding the mechanism of wound healing

The healing of an acute wound (post-operative wound) proceeds through to healing "in an orderly and timely reparative process". Orderliness refers to the healing sequence of inflammation, angiogenesis, matrix deposition, wound contraction, epithelialisation, and scar remodelling (18). A critique of comprehending the process of surgical wound healing elucidates that it takes place via deep synergy of diverse overlapping phases: haemostasis, inflammation, proliferation, and tissue remodelling or resolution. Interferences or disruption interruptions, oddities or undue delay in this sequence can prolong the process and can lead to delayed wound healing or a non-healing chronic wound (19). In a healthy adult the stages of wound healing as depicted in the literature include swift stability in attaining haemostasis, appropriate inflammatory response, cell differentiation mainly (mesenchymal) followed by the spread and migration of differentiated cells into the wound site. Neo angiogenesis brings in more blood supply to the wound and it is then followed by rapid reepithelialization and collagen cross linking, providing ample strength to the healing tissues at the site of surgical wounds (20). Wound healing is described as consisting of three phases irrespective of the factors that resulted in the injury: the inflammatory, the proliferative and the remodelling phases (21-23).

The first stage constitutes the body's first line response to the injury and its immediate reaction triggers the localised release of inflammatory mediators thereby inducing a local vasodilation at the site of injury which then aids an influx of phagocytic leucocytes, such as neutrophils and macrophages, which are essential in digesting bacteria and autolysing devitalised tissue. The inflammatory phase of wound healing is responsible for the classical signs of inflammation that occur in response to an injury: erythema, heat, oedema, pain and decreased function.

In the second stage, the wound rebuilds itself in the proliferative phase. The major contributory steps in this phase include filling the wound surface with granulation tissue comprised of collagen and extracellular matrix, and angiogenesis starts to set in. In this stage, the wound edges approach each other via contraction of epithelial tissues. The finishing of this stage is marked by epithelial cells fully resurfacing the wound.

The final stage is remodelling which starts when the wound is closed and attains tensile strength with the help of collagen fibres remodelling and reorganizing themselves. This phase also witnesses devascularisation of the wound and surrounding structures returning to their original state of blood supply (24).

Conceptual understanding of stages of healing (*Vrana Ropana*) as per Ayurveda

The process of the stages in wound healing can be drawn from the references where Acharya *Susruta* details the type of *Vrana* based on evident features of wound progression towards healing.

1. Dushta *vrana*. Acharya's first description of features of a non-healing wound include that it is innately affected by Tridoshas and has purulent and profuse discharge, a foul odour. The discharge shows traces of blackish, greenish, and yellowish colours and inflicts pain. All these features are suggestive of an infected non-healing ulcer or, in a post-operative wound, they are signs of the wound being microbially infected.

2. Shuddha *vrana*. A conceptual understanding includes that this type of wound is actually devoid of doshic involvement with minimal pain and the features of the wound include pinkish granulation tissue with minimal discharge or sloughing at the wound base. These are, in fact, features of an intentional wound created as in a surgical procedure. They are also comparable to the clinical features indicative of the process of wound healing.

3. Ruhyamana *vrana* – In this stage in the progression of wound healing the wound is pale or grayish in colour and the margins are healthy. There is minimal discharge or evidence of sloughing. The borders are devoid of induration and granulation tissue from around the margins and floor indicates an uneventful healing process comparable to the repair phase of contemporary understanding of wound healing.

4. Rudha *vrana* – This stage can be perceived as the final phase of healing of a wound. There is an approximation of wound edges and the beginning of scar formation with the wound and periphery attaining an even skin tone with no swelling or pain in the wound (25).

Care of post-operative wounds

The key components in facilitating an optimal wound healing are attained mainly by reviewing the post-operative wound from time to time. Care should be given to include thorough cleaning and wound dressing. It is essential to recognize challenges early and provide effective treatment for the complications that are associated with wound healing. Whatever principles are adopted in wound care, the aim is ideal wound healing without complications and with the best aesthetical and functional results (26).

Wound Cleaning: The protocol includes cleansing of a wound which is attained by clearing the wound of debris, e.g., devitalised tissue or excessive exudates, which may otherwise delay wound healing (27). Wound irrigation should be gentle to avoid further tissue trauma and should be done with warm saline or water (as per NICE recommendations) using a syringe, rather than swabbing or bathing, which maintains an optimum healing environment (28).

Wound dressings: Dressings are considered another important step in diligent efforts to achieve wound healing as they sustain a moist wound environment while at the same time absorbing excess exudates that might lead to maceration of the wound. Dressings in place also provide a physical barrier against bacterial or fluid contamination, and can be adherent to the skin but atraumatic on removal (29).

Care of wounds in Ayurveda

The sequence of wound care in Ayurveda is detailed in *Paschat Karma* and explained by Acharya *Susruta* in *Agropaharaneeya Adhyaya* in *Sutra Sthana*. He mentions that post operatively after consoling the patient by sprinkling cold water on the wound, the post-surgical wound must be slightly circumferentially pressed to remove all clots and exudates, and to approximate the edges of the wound to make the surface even. The next stage includes *vrana prakshalana* (irrigating the wound) with *Kashayas* (medicated water) which include *tikta* rasa and *sheeta veerya*. Then the wound is mopped with sterile gauze and medicated *Alepa* (wound dressings) containing *tila kalka*, *madhu*, *sarpi* should be made into a wick and placed in the wound. This facilitates maintaining wound moisture and also provides adequate draining of collected exudates. A paste of medicines effective in healing *sadyo vrana* should be smeared over the wound and the wound should be covered with thick dressings secured by bandaging. Additionally, it is also advised to do *dhoopana*, a proven technique to attain a sterile environment so as to promote ample healing (30).

Importance of Raksha Karma.

Acharya Sushruta explained *Dhoopana* as fumigation with *rakshoghna Dravyas* e.g., *Guggulu* (*Comiphora mukkul*), Agaru (*Aquilaria agollocha*), Sarjarasa (*Vateria indica*), Vacha (*Acorus calamus*), Sarshapa (*Brassica nigera*), Lavana, Nimba (*Azadirachta indica*) mixed in cow ghee (31). He also mentions the chanting of mantras and advocates various dos and don't's for *Vranita* (the wounded).

Practising post-operative pain management

Acharya *Susruta* mentioned that severe pain which is caused by Shastras (surgical instruments) can be managed by irrigation with lukewarm ghee processed with Yashti *Madhu* as a general line of management (32). In wounds that are by Vyadhana, Karma, Acharya advocates irrigation of wounds with Ama Taila (unprocessed, non-heated sesame oil) (33). In wounds created by thermal cautery, the wound should be smeared with a combination of *madhu* and Sarpi (34). He also mentions the use of medicated ghee prepared from tug*akshi*ri (*Curcuma angustifolia* Roxb), plaksha (*Ficus virens*), Chandana (*Santalum album*), gairika (red oxide of iron) and amruta (*Tinospora cordifolia*) (35). For *vrana* caused by Kshara karma, Acharya recommends washing with Amla varga Dravyas and lepana with *tila kalka*, *Madhu* and ghrita Sushruta (36). In wounds inflicted by treatment with jalouka, after blood-letting smearing the wound with Shata dhouta ghrita is advised (37). In the bleeding in wounds caused by application of blood-letting therapy, the control of haemorrhaging is attained by four principles, mainly sandhana by irrigating with Kahsyaa rasa Dravyas, sheet veerya dravyas. Skandana application of Hima and dahana by Agni karma of the bleeding vessel and Pachana is attained by sloughing the blood and thus forming clots by application of Bhasma. Sushruta (38).

Why Tila, *Madhu*, ghrita and Yashti *Madhu*

Honey is widely used as topical wound dressing and its efficacy is evidenced by various meta-analyses of use of honey as a topical wound dressing agent (39). The mode of action could be explained by its anti-oxidant, anti-bacterial and anti-inflammatory properties. Honey has numerous properties: a natural anti-inflammatory effect, a stimulatory effect on granulation tissue and an antibacterial effect (against many strains of bacteria, e.g., Staphylococcus, Streptococcus and Helicobacter pylori) (40). Honey also has high acidity which provides secondary benefits in addition to the osmotic effect in addition to its anti-oxidant properties and its hydrogen peroxide content. Thus the use of honey leads to improved wound healing in acute cases, pain relief in burn patients and decreased inflammatory response in many patients (41). Cow ghee has antioxidant properties as it contains fat-soluble vitamin E and beta carotene (42). It also possesses antibacterial, anti-inflammatory, and antiseptic properties that are beneficial in treating various skin-associated problems. Because of that, it helps treat blisters, inflammatory swellings, and wounds, helping to speed the healing process (43).

Tila (*Sesamum indicum*) kalka aids in the healing of wounds by accelerating skin border contraction. Also it helps in achieving an even covering of granulation tissue and regeneration of epidermis. Sesame oil contains active ingredients with anti-oxidant and antibacterial properties, especially in the inflammatory phase due to its acidic PH. Acidic Ph also helps new skin growth by promoting cell migration and proliferation. Wound healing is finally brought about by the fibroblast activity, and collagen restructuring (44).

Yashti*madhu* has proven healing, anti-ulcerogenic, anti-inflammatory and skin regeneration activity. Sodium glycyrrhizate possesses anti-ulcer activity and stimulates regeneration of skin. Yashti*madhu* contains glycyrrhizin acid and ammonium salt [GA] which has demonstrated ulcer healing activity according to some pharmacological articles (45). The effect of yashti*madhu* on post operation wounds was tested in previous studies where it was shown to give positive results following the use of Yashti *Madhu* on post-operation wounds. It reduces the number of inflammatory cells and enhances fibroblasts maturation and tissue alignment and ulcer healing where it has shown an increase in the percentage of ulcer contraction and epithelization (46).

DISCUSSION

The review of ancient writings by Acharya *Susruta* paves a pathway for critical thinking which encompasses versatile aspects of wound healing including the comprehensive perspectives of the

role of mental, emotional and spiritual wellbeing of the patient rather than focussing on the physiology of wound healing and pathophysiology related to surgical infections, dehiscence and other similar challenges. This comprehensive approach however, is often disdained. The evidence of polyherbal formulations with essential components containing pharmacologically active substances are still a grey area and requires exhaustive reviews and research, including clinical trials. The role of advocated diet and lifestyle changes are also of utmost importance, but are typically often overlooked as patient education is a necessary compontent in this regard. The type of wounds caused by surgical instruments, medicinal leech therapy, thermal and caustic cautery have all been identified. This sort of detailed identification of mechanisms affecting post-surgical wounds and entrusting different protocols for the same should be given due consideration so that wound healing approaches to various wounds can be tailor-made after surgeries. Moreover, research results support the essential role of improving patient morale and self-dependency to post-operative care. There exists a continuing need for multidisciplinary efforts to provide safe and effective use of herbal compounds which are explained by Acharyas and to timely integrate this traditional wisdom into contemporary practices. The role of integrating this know-how about wound care can have complimentary results that aid in optimizing post-operative wound outcomes.

CONCLUSIONS

Comprehension of the mechanisms supporting optimal wound healing is the paramount need of the hour. Various ambiguities still exist in spite of exhaustive research on the subject. There is a need to extend the review of conventional treatises to explore concepts regarding various methods used in post-operative wound healing. The basic principles encompass methodical assessment, adopting modalities for wound cleansing and identifying signs of wound healing and, most of all, recognition of any red flags indicating possible wound complications and the need for timely interventions.

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REFERENCES

1. Pinto A, Faiz O, Davis R, Almoudaris A, Vincent C. Surgical complications and their impact on patients' psychosocial well-being: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e007224. PubMed PMID: 2688323
2. Tevis SE, Kennedy GD. Postoperative complications and implications on patient-centered outcomes. J Surg Res. 2013;181:106-13.
3. Broex ECJ, van Asselt ADI, Bruggeman CA, van Tiel FH. Surgical site infections: how high are the costs? J Hosp Infect. 2009;72:193-201.
4. Kusachi S, Kashimura N, Konishi T, Shimizu J, Kusunoki M, Oka M, et al. Length of stay and cost for surgical site infection after abdominal and cardiac surgery in Japanese hospitals: Multi-center surveillance. Surg Infect (Larchmt). 2012;13:257-65.
5. Graf K, Ott E, Vonberg RP, Kuehn C, Schilling T, Haverich A, et al. Surgical site infections-economic consequences for the health care system. Langenbeck's Arch Surg. 2011;396:453-9.
6. Merkow RP, Ju MH, Chung JW, Hall BL, Cohen ME, Williams MV, et al. Underlying reasons associated with hospital readmission following surgery in the United States. JAMA. 2015;313:483-95.
7. Tartari E, Weterings V, Gastmeier P, Rodríguez Baño J, Widmer A, Kluytmans J, et al. Patient engagement with surgical site infection prevention: an expert panel perspective. Antimicrob Resist Infect Control. 2017;6:45. PubMed PMID: 28507731
8. Pruitt Jr BA, McManus AT, Kim SH, Goodwin CW. Burn wound infections: current status. World J Surg. 1998;22:135-45.
9. Kassin MT, Owen RM, Perez SD, Leeds I, Cox JC, Schnier K, et al. Risk factors for 30-day hospital readmission among general surgery patients. J Am Coll Surg. 2012;215:322-30.
10. Dutta Kaviraja AD. *Sushruta Samhita* of *Acharya Sushruta*, Chikitsa Sthana, 1st chapter, verse 8. Varanasi: Chowkhamba Sanskrit Sansthan; 2007. p. 397.
11. Mengistu DA, Alemu A, Abdukadir AA, Mohammed Husen A, Ahmed F, Mohammed B, et al. Global incidence of surgical site infection among patients: systematic review and meta-analysis. Inquiry. 2023;60:469580231162549. PubMed PMID: 36964747
12. Onyekwelu I, Yakkanti R, Protzer L, Pinkston CM, Tucker C, Seligson D. Surgical wound classification and surgical site infections in the orthopaedic patient. J Am Acad Orthop Surg Glob Res Rev. 2017(3):e022. PubMed PMID: 30211353

13. Gorvetzian JW, Epler KE, Schrader S, Romero JM, Schrader R, Greenbaum A, et al. Operating room staff and surgeon documentation curriculum improves wound classification accuracy. Heliyon. 2018;4(8):e00728. PubMed PMID: 30109278
14. Acharya YT. *Sushruta Samhita*. Varanasi: Chaukhamba Sanskrit Sansthan; Reprint 2009. *Sutra Sthana* 23/5,6,12.
15. Shastri A. *Susruta* samhita – Ayurveda tattva sandipika commentary. Reprint edition. Varanasi: Chaukhambha Sanskrit Sansthan; 2018. Sushruta Chikitsasthana 1/3.
16. Shastri A. *Susruta* samhita – Ayurveda tattva sandipika commentary. Reprint edition. Varanasi: Chaukhambha Sanskrit Sansthan; 2018. Sushruta Sutrasthana 22/6.
17. Tripathi B. Charak Samhita – Charak Chandrika, Hindi Commentary Vol I and II. Reprint edition. Varanasi: Chaukhamba Subharti Prakashan; 2003. Charak Chikitsa Sthana 25/6.
18. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol. 1994;130:489-93.
19. Gosain A, DiPietro LA. Aging and wound healing. World J Surg. 2004;28:321-6.
20. Mathieu D, Linke J-C, Wattel F. Non-healing wounds. In: Mathieu DE, editor. Handbook on hyperbaric medicine. Netherlands: Springer; 2006. p. 401-27.
21. Gilmore MA. Phases of wound healing. Dimens Oncol Nurs. 1991;5:32–4.
22. Broughton G 2nd, Janis JE, Attinger CE. Wound healing: an overview. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):1e-S-32e-S. PubMed PMID: 16801750.
23. Hunt TK, Hopf H, Hussain Z. Physiology of Wound healing. Adv Skin Wound Care. 2000;13:6–11.
24. Hunt TK, Hopf H, Hussain Z. Physiology of Wound healing. Adv Skin Wound Care. 2000;13:6–11.
25. Acharya YT, Sri Dalhanacharya. Nibandha Sangraha *Susruta* Samhita. Varanasi: Chaukhamba Sanskrit Sansthan; 2009. *Sutra Sthana*, 23/13/18-20.
26. Singer AJ, Dagum AB. Current management of acute cutaneous wounds. N Engl J Med. 2008;359:1037–46.
27. Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. J Int Med Res. 2009;37:1528–42.
28. Ennis WJ, Valdes W, Salzman S, Fishman D, Meneses P. Trauma and wound care. In: Morison MJ, Ovington LG, Wilkie K, editors. Chronic wound care. A problem-based learning approach. London: Mosby Elsevier Limited; 2004. p. 291–307.
29. Ruszczak Z, Schwartz RA, Joss-Wichman E, Wichman R, Zalewska A. Medscape reference: surgical dressings [Internet]. [cited 2013 July 13]. Available from: emedicine.medscape.com/article/1127868-overview#showall
30. Patil VC, NM Rajeshwari. *Sushruta Samhita* with English translation of text and Dalhana's commentary with critical notes. Varanasi: Chaukhambha Publications; 2018. Vol 1, p. 70.
31. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; 2008. p. 5/18.
32. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; 2008. p. 5/42.
33. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; 2008. p. 16/7.
34. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; Reprint 2008. p. 12/13.
35. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; 2008. p. 12/23,24.
36. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; Reprint 2008. p. 11/19-21.
37. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; Reprint 2008. p. 13/23.
38. Sushruta. *Sushruta Samhita* with Nibandha Sangraha, Nyayachandrika Commentary, Chikitsa Sthana. Reprint edition. Varanasi: Chaukhambha Orientalia; Reprint 2008. p. 14/39.
39. Mwipatayi BP, Angel D, Norrish J, Hamilton MJ, Scott A, Sieunarine K. Review. Int J Pharm Biol Arch. 2013;4:833-41.
40. Namias N. Honey in the management of infections. Surg Infect (Larchmt). 2003;4:219-26.
41. Yaghoobi R, Kazerouni A, Kazerouni O. Evidence for clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory, anti-oxidant and anti-viral agent: a review. Jundishapur J Nat Pharm Prod. 2013; 8:100-4.
42. Uppalwar S, Aeri V, Arora A. Evaluation of wound healing properties from five traditional medicinal plants with cow ghee. J Med Pharm Innov. 2014;1:24–8.
43. Dunphy JE, Edwards LC, udupa KN. Wound healing; a new perspective with particular reference to ascorbic acid deficiency. Ann Surg. 1956;144:304–17.
44. Mwipatayi BP, Angel D, Norrish J, Hamilton MJ. Review. 2004. 45. Physico-chemical evaluation of yashthi*madhu* ghrita. Int J Med Health Sci. 2014;1:1-24.
46. Gilmore MA. Phases of Wound healing. Dimens Oncol Nurs. 1991;5:32–34.