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Original Article Open Access

A Method for Teaching "Safe Listening" Integrated with Early Clinical Exposure for Third-Year Medical Students

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ABSTRACT

OBJECTIVES The primary objective of this study is to describe a method for teaching "Safe Listening" integrated with early clinical exposure (ECE). Additionally, the study aims to assess preferred listening levels (PLLs), expected output levels, and classroom noise levels.

METHODS Retrospective cross-sectional study. After pre-activity instruction, medical students were grouped into classrooms. The noise level in each classroom was measured using a sound meter application both in quiet situations and during conversations while the medical students were listening to their personal listening devices (PLDs). A calibrated finger rub auditory screening test and a tuning fork test were conducted and PLLs were recorded. The students discussed the findings and rated their satisfaction with the process at the end of the activity.

RESULTS The average PLL of the 171 third-year medical students was 59.00 ± 7.38 dBA. The classroom noise level was 49.66 ± 8.45 dBA in quiet periods, and 77.51 ± 10.05 dBA during conversation and while listening to PLDs via earphones. In quiet periods, 97.65% of the students could hear finger rub in both ears. The average satisfaction score after the activity was 82.57 ± 13.14%.

CONCLUSIONS Practice with hearing tests and self-checks of PLLs introduced exposure to clinical learning together with awareness of safe listening. PLLs of medical students and satisfaction with the activity were in the favorable range.

KEYWORDS early clinical exposure, medical education, safe listening, preferred listening level

INTRODUCTION

To help bridge the gap between preclinical and clinical medical training, early clinical exposure (ECE) is a well-documented teaching-learning method for helping medical students transfer basic scientific knowledge into a clinical context (1, 2). ECE helps medical students improve their academic performance, develop communication skills, increases their motivation towards self-directed learning, enhances their appreciation of medical professionalism, fosters emotional development and empathy, helps develop an empathic and holistic attitude, and increases understanding of working in a team (1-3).

A variety of clinical teaching-learning activities in the preclinical period can be conducted as ECE,

The study was presented in a short communication session in Asia Pacific Medical Education Conference (APMEC), Singapore, on 22 - 23 May 2023

e.g., observation, small group teaching, clinical bedside teaching, supervision and feedback, self-learning, and case-based learning. Settings in ECE are divided into three groups: classroom, hospital-based, and community settings. The classroom setting is the basic and most convenient form of ECE. Strategies used in the classroom setting include the arrangement of patients in the classroom, preparation of case scenarios, and discussion of clinical materials (1-4).

During the COVID-19 pandemic, all preclinical courses were switched to an online mode. As a result, medical students have had increased earphone usage and increased listening time via personal listening devices during online study. The author considered that medical students should be aware of their hearing health and that they would benefit from clinical experience with hearing tests.

Safe listening refers to listening behavior that does not put hearing at risk of irreversible hearing damage (5). More than one billion young people put themselves at risk of permanent hearing loss by listening to loud sounds (6). In 2015, the World Health Organization (WHO) launched the Make Listening Safe initiative that aims to promote safe listening and reduce the risk of hearing loss due to loud recreational sounds. The "Make Listening Safe Workgroup" is a group working on promoting and supporting programs and materials for safe listening. Its goal is to "create a world where nobody's hearing is put in danger due to unsafe listening" (7). In 2019, the WHO published the WHO-ITU Global standard for safe listening devices and systems which offers recommendations related to safe listening features on personal audio devices. In 2022, WHO published the "mSafeListening Handbook" which provides evidence-based information for the promotion of safe listening behaviors and prevention of hearing loss as well as guidance on how to develop, integrate, implement and evaluate a national mSafeListening program (6). Awareness of self-listening levels is the first step to reducing the risk of sound exposure to loud noise. "Increasing awareness of the importance of safe listening and changing behavior for the target group (young people)" is one of the main objectives of the Make Listening Safe Workgroup (7).

Self-reported preferred listening level (PLL) is a comfortable listening level (0-100%) of the maximum volume setting of a personal listening device (PLD). The formula to convert self-reported PLD volume to decibels (expected output) is 0.53 x% + 34, where "x" is a 10-100 scale for setting volume levels (8).

Teaching "safe listening" integrated with ECE activities should help medical students to learn about hearing screening and the effects of environmental noise on listening levels and checking an individual's PLL as a way of raising awareness of safe listening. This study aimed (1) to describe an ECE activity integrating safe listening content and (2) to assess PLLs, expected output levels, and classroom noise levels.

METHODS

This retrospective cross-sectional observational study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University (CMU), the first regional medical school in Northern Thailand (study code ENT-2565-09065). Data was self-recorded in a data collection form by the enrolled students during the in-class activity. This ECE activity was set up for the third-year preclinical medical students at the end of the 2021 semester prior to exposure to the first-year clinical experience. Prior to the activity, instructions and orientation were provided in a guiding document. All third-year preclinical medical students were recruited. The students were divided into small groups of nine to ten students per group. Each group performed the ECE activity in a separate classroom. The classroom size was 3.62 x 3.97 x 3.0 m (width x length x height). The on-site activity was supervised by the coursework instructor (the first author) under COVID-19 precautions. One fifth-year medical student was assigned as a teaching assistant in each classroom. All students brought their PLDs and earphones. They were told to download a sound meter application before attending the class. The smartphone application was either "Sound Meter" in the android system or "NIOSH Sound Level Meter" in the IOS system. After the students were in the classroom, they were paired and the ECE activity started. The 30-minute activity was split into three ten-minute periods.

In the first ten minutes of the ECE activity the following steps were conducted in a quiet environment as follows:

1. The noise level in the classroom was measured using the sound meter application.

2. A screening hearing test was performed using the calibrated finger rub auditory screening test (CALFRAST) (9).

3. The Weber test was performed both with and without pressure on the right tragus. Closure of the right ear canal created the right conductive hearing loss.

4. The PLL was recorded while listening to the "Med CMU" song (downloaded from YouTube at https://www.youtube.com/watch?v=D3hu__krFeY) via their PLDs and earphones.

5. The level of loudness (too soft, comfortable, too loud) was recorded while listening to the "Med CMU" song at 60% of maximum volume which is the upper limit for safe listening.

In the second ten minutes, the students held a conversation. The activity included the following steps:

1. The noise level was measured in the classroom using the sound meter application with and without wearing earphones at PLL.

2. The screening hearing test was performed with CALFRAST while wearing earphones and listening to the Med CMU song at PLL. This step aimed to initiate appreciation of how the signal-to-noise ratio can affect hearing ability.

In the final ten minutes, the students discussed the findings among themselves and rated their satisfaction with the activity. Two opened-end questions were then given for the students to answer on a data collection form: "What you have learned today?" and "Please give your comments and feedback".

RESULTS

Of the 224 third-year medical students, 221 (98.7%) were enrolled in the class and were divided into 24 small groups. The completed data of 171 students were analyzed.

The sound meter applications were NIOSH 147 (86.0%), and Sound Meter 24 (14.0%). The types of earphones used in the class were earbud 101 (59.06%), in-ear 58 (33.92%), supra-aural 2 (1.17%), and noise-cancellation 10 (5.85%). While listening to the Med CMU song at a listening level of 60% of maximum volume, the students reported whether the level was too soft 7 (4.09%), comfortable 53 (30.99%), or too loud 111 (64.91%). PLL while listening to the Med CMU song with their listening devices with earphones. Expected output levels were calculated using a formula proposed by Williams et al. (8) as shown in Table 1 and Figure 1. The PLL is a 0-100 scale, where 100% is equal to the maximum volume of a PLD. The expected output levels among the four different types of earphones showed no differences (p-value = 0.73). Classroom noise level and CALFRAST results in the three situations are shown in Table 2.

The average satisfaction rating of the in-class activity was 82.57 ± 13.14% (mean ± SD), with a range of 50-100. In the opened-ended questions, the student's reflections about "What did you learn today?" included:

- How to perform a physical examination and screening hearing tests using the CALFRAST and Weber tests in the clinical year.

Table 1. Preferred listening levels and expected output using a personal listening device with earphones

Type of earphone (number of students)	Preferred listening level (%) Mean±SD (range)	Expected output level (dBA) Mean±SD (range)
Earbud (101)	47.32±13.79 (10-76)	59.08±7.31 (39.30-74.28)
In-ear (58)	47.62±13.69 (25-90)	59.24±7.25 (47.25-81.70)
Supra-aural (2)	50.00±28.28 (30-70)	60.50±14.99 (49.90-71.10)
Noise-cancellation (10)	42.40±15.73 (25-70)	56.47±8.34 (47.25-71.10)
Average (171)	47.16±13.90 (10-90)	59.00±7.38 (39.30-81.70)

Table 2. Classroom noise level and CALFRAST results in the three situations

	Quiet	Conversation	Conversation and listening to the song
Classroom noise level (dBA)	49.66±8.45	71.88±9.43	77.51±10.05
Mean ± SD (range)	(35-72)	(40-95)	(45-95)
CALFRAST results (% heard in both ears)	97.65	-	52.05

CALFRAST, calibrated finger rub auditory screening test

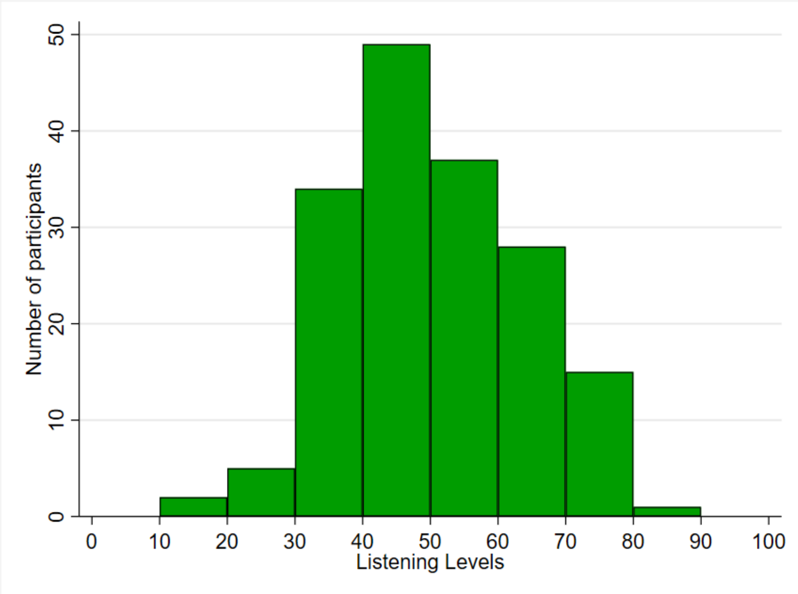

Figure 1. Histogram of Preferred Listening Levels

- How to perform the tuning fork test while pressing the tragus created conductive hearing loss.
- How to use smartphone sound meter applications to check environmental noise levels.
- How to check their PLLs: they need to speak louder in a noisy environment and while using earphones via the PLDs. They should reduce their listening level. They should limit their use of earphones. They were concerned about loss of hearing if they listened to sound that is too loud.

Positive comments and feedback included:

- They enjoyed participating in the ECE activity.
- They were excited to have had new experiences during the ear and hearing examination.
- They felt the activity should be continued the next year.

Negative feedback included:

- The classroom was too small, there were too many students in the classroom, and the classroom was too noisy.
- The activity time was too short: 10-15 minutes is need.
- The broken air-conditioner (in one classroom) was disruptive.
- There were not enough tuning forks.
- The online pre-activity instruction should be more explicit and should not be conducted too close to the on-site activity.
- A post-activity summary should be included.

DISCUSSION

Medical students are future doctors or healthcare providers. They are expected to be role models and to exemplify healthy lifestyle behaviors for patients (10). If they exemplify the health advice they give to patients, that should provide greater motivation for their patients to follow their counseling (11). In 1998, the WHO Regional Office for Europe published guidance on establishing and developing a health-promoting university (12). The ASEAN University Network (AUN) Health Promotion Network also published the AUN Healthy University Framework in 2017 (13). In the past, healthy university policies have been mainly focused on smoking, alcohol or drug use, diet, exercise, and stress. Hearing health promotion policies should also be initiated in medical schools and health science faculties.

To follow the social distancing policy during the COVID-19 outbreak, online teaching was required. Increased use of earphones via the PLDs amplified the risk of noise-induced hearing loss (NIHL). Damage to hair cells in the inner ear by noise is irreversible. WHO has estimated that 430 million people live with disabling hearing loss requiring rehabilitation services. Globally, more than one billion young people put themselves at risk of permanent hearing loss by listening to loud sounds (6). The US National Health and Nutrition Examination Survey reported the prevalence of hearing loss in 4,305 adolescents 12-19 years of age. Between the years 1988-1994 and 2005-2006, the overall prevalence of exposure to loud noise or listening to music through headphones in the previous 24 hours increased significantly from 19.8% to 34.8% (14). Younger people more frequently listen to music at a higher volume than do to older people (15). If possible, conventional audiometry should be performed to compare the prevalence of NIHL before and after the increased use of PLDs in online teaching during the COVID-19 outbreak. Difficulty in communication due to hearing loss impacts individuals, their families, society, and the economy. Hearing loss is an invisible handicap. If people at risk were aware of their self-listening level, they would try to reduce their exposure to loud sounds and would consider adopting safe listening behavior. Detection and identification of high-risk noise exposure affecting by young people is very important for primary prevention. Medical students, as young future doctors, should be the first target group for the implementation of safe listening programs and should be enrolled in a hearing health promotion team.

In this study, the average PLL (47.16 ± 13.9%) and expected output level (59.00 ± 7.38 dBA) from PLDs of third-year medical students in a noisy situation were lower than in previous reports. Paping et al. reported two studies of Generation R, population-based prospective cohort studies from fetal life until young adulthood in Rotterdam, the Netherlands. The mean PLL from postal questionnaires of 237 subjects (aged 12-15 years) was 54.5 ± 18.1% (16). The mean PLL from the PLDs of 314 subjects (aged 13 years 7 months ± 5 months), measured using a newly developed smartphone application, was 55.0 ± 17.9% (17). The mean PLLs of 183 middle school students and 233 high school students in Ulsan, Korea reported by Lee et al. (2021) was 70.13 ± 8.01 dB (18). Gilliver et al. reported the mean self-reported PLD listening volume from an online survey of 5,371 Australians aged > 15 years (mean age 31.4 years) to be 53.3 ± 21.1% (19). Portnuff et al. reported the PLL of 29 normal-hearing subjects (aged 13-17 years) in Denver, Colorado, USA, using earbuds, in-ear, and supra-aural earphones. The mean comfortable PLL collected from the subjects' questionnaire was 55 ± 17.2%. The average PLL across earphone types under 70 dB under pink noise conditions in the laboratory was 79.3 ± 5.2 dBA (20). Although there was no difference in expected output levels of PLLs among four different types of earphones in this study, the lowest PLLs were observed with the use of noise cancellation earphones.

Contrary to Hoshina et al., they found that canal earphones with noise canceling showed the lowest PLLs among the three earphone types used by 23 subjects (age 20-40 years) (21). This difference may have resulted from the activity in the present study having been conducted in small classrooms with the doors closed. Even though the average PLL was lower than 60% and 95.9% of the third-year medical students reported the sound at a level of 60% of maximum volume being comfortable or too loud while listening to the song, the students may require louder PLLs outside the classroom. Safe listening behavior should be encouraged.

The average satisfaction score after the in-class activity in this study was high. The authors encourage medical educators to apply this ECE teaching method integrated with self -directed learning about safe listening for their settings. Before setting up the activity, the instructor and the faculties involved should consider classroom size, classroom condition, number of students in each classroom, number of tuning forks needed, appropriate length of time for the activity, clarification of pre-activity instructions, and a review of post-activity conclusions.

This study had limitations. It was a cross-sectional study of 171 third-year medical students at CMU in northern Thailand. Although this was a retrospective study, pre-activity instruction was provided and data were collected using data collection forms. The ECE activity was performed in small classrooms with only nine to ten students in a room. The results may not apply in larger populations or in an environment outside classrooms, in other preclinical and clinical classes in other medical schools or with other faculties. The environmental sound was measured by two applications, "Sound Meter" in the android system and "NIOSH Sound Level Meter" in the IOS system, without the use of a standard sound level meter. However, both applications are validated smartphone-based applications that can be used for measuring ambient noise levels. Both applications are listed as validated sound-level apps in the WHO ear and hearing survey handbook (22). The SoundMeter app showed good agreement in

A-weighted sound levels, with a mean difference of -0.52 dBA from the reference values and mean differences within ± 2 dBA of the reference measurements (23). The use of smartphone applications is appropriate for implementation of this ECE activity in other safe-listening initiation programs in other settings. In conducting this ECE activity, the authors planned to instill awareness of listening levels and classroom noise levels that can affect audibility. The students should understand the methods for measuring noise levels and monitoring their PLLs. This study did not focus on the accuracy of the noise level or compare the noise levels measured using the application and those measured using a standard sound level meter. The classroom noise levels shown in Table 2 do not indicate the actual noise levels. To obtain accurate noise level measurements, calibration of the applications should be performed before measuring.

CONCLUSIONS

The majority of the students were satisfied with this ECE activity and requested that the activity be continued the next semester. The students appreciated gaining new experience with hearing tests and measuring PLLs and noise levels in quiet and noisy environments. Increasing the room size, decreasing the number of students per group, clarifying the pre-activity and post-activity summarization and provision of a sufficient number of tuning forks should improve student satisfaction. Even though the average PLL was lower than that in previous reports and was less than 60% of the maximum volume, awareness of safe-listening behavior should be encouraged and hearing health promotion should be initiated as a primary hearing loss prevention program. Using a low level of PLL encourage medical students to be a good role model of healthy hearing behavior.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Original Article Open Access

The Precision of Lumbar Spine BMD and TBS on Different Vertebral Combinations

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ABSTRACT

OBJECTIVE The objective of this study is to compute the precision and LSC of BMD and TBS at the lumbar spine using dual-energy X-ray absorptiometry in different vertebral combinations.

METHODS Thirty female participants (age 58.8 ± 4.0 years, height: 155.0 ± 5.2 cm, weight: 57.4 ± 8.6 kg and BMI: 23.9 ± 3.6) were scanned at the lumbar spine twice in the same day using DXA. The precision and LSC of BMD and TBS were computed in terms of the RMS-SD and %CV using the ISCD Advanced Precision Calculation Tool.

RESULTS The precision and LSC of BMD of the 4 vertebrae combinations showed the best precision and also showed a similar trend (0.005 g/cm^2 and 0.62%, 0.013 g/cm^2 and 1.71%), respectively. For TBS, the precision and LSC followed a similar pattern as BMD but was inferior to those of BMD. The %CV LSC of BMD for all vertebrae combinations did not exceed 5.3% as recommended by ISCD (15). The %CV LSC of TBS for 2-4 vertebrae combinations were within 5.8% with the exception of the individual vertebra which was unacceptable (%CV range 6.17-8.98).

CONCLUSIONS All vertebrae combinations had an acceptable level of precision and LSC for BMD monitoring. However, the precision and LSC of TBS were inferior to those of BMD, and individual vertebra were not appropriate for TBS monitoring.

KEYWORDS precision, least significant change (LSC), bone mineral density (BMD), trabecular bone score (TBS)

INTRODUCTION

Dual-energy X-ray absorptiometry (DXA) is the current gold standard for the clinical diagnosis of osteoporosis based on the measurement of bone mineral density (BMD) for the diagnosis of osteoporosis and monitoring of changes in BMD over time (1, 2). DXA measurements at the central skeletal site (lumbar spine and proximal femur) are recommended for diagnosis of osteoporosis. Lumbar spine measurements can provide BMD values, which quantify the amount of minerals in specific volumes of bone (3). The lumbar spine is effective for monitoring treatment response due to its higher proportion of trabecular bone in the vertebral bodies and it also adheres to the World Health Organization (WHO) operational definition of osteoporosis and osteopenia (4). DXA measurements of the lumbar spine also provide trabecular bone score (TBS) values that are derived from the same region of interest (ROI). TBS is a non-invasive technique that evaluates bone quality by analyzing gray-level variations in lumbar spine images to project a 2-dimensional image of the 3-dimensional (3D) structure (5). TBS holds the potential to monitor the effects of anabolic therapy involving drugs such as teriparatide and abaloparatide (6).

Because DXA measurements are useful for monitoring changes over time of disease progression and treatment response, reproducibility and precision are essential. To determine whether a difference between measurements is statistically significant (indicative of a true change) or falls within the examination's range of error, the ISCD has recommended the use of precision and least significant change (LSC) values. The precision of DXA measurements is expressed as root mean square standard deviation of BMD and TBS in absolute terms (g/cm^2). It is sometimes expressed as CV or %CV, but this is less desirable due to variation in these values over a range of measured BMD (7). The LSC represents the smallest difference between successive measurements. This threshold value is set equal to the upper limit of the 95% confidence range for the mean value of the differences between measurements and can be mathematically calculated (8). The difference is normally considered to be statistically significant when it exceeds the LSC.

When performing DXA measurements on the lumbar spine, the image should be clear and devoid of artifacts. Artifacts can be inside or outside of patients and both can impact BMD interpretation. While external artifacts such as jewelry or the type of clothing textiles can be avoided through careful pre-scan questions and perceptive observation by technologists, internal artifacts such as vertebral fractures, aortic calcification, peacemakers and surgical clips cannot be removed (9, 10). In cases where the lumbar spine image is compromised by internal artifacts or when it displays a T-score discrepancy greater than 1.0 compared to adjacent vertebrae, the International Society for Clinical Densitometry (ISCD) recommends excluding the affected individual vertebra from the analysis based on specific criteria. However, diagnostic classification requires a minimum of two vertebrae (11).

The aim of this study is to evaluate the precision and LSC values of BMD and TBS at the lumbar spine using DXA measurements for different vertebral combinations of excluded vertebrae. These values assist physicians in making more accurate interpretation of results, thereby facilitating informed decision-making.

METHODS

Study participants

In this study, 30 female volunteers aged between 56 and 67 years were recruited from the staff of our hospital. To help ensure reliable and accurate measurements, participants with any anatomical abnormalities that could interfere with the interpretation of spine images, e.g., lumbar spine fixators, a history of lumbar spine fractures, severe lumbar scoliosis, oral contrast administration within the past 7 days, or the possibility of pregnancy, were excluded. All participants provided signed informed consent before participating in the study. The demographic characteristics of the participants are shown in Table 1. This study received approval from the Institutional Review Board (IRB) of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (Research Ethics Code COA. MURA 2022/677).

DXA measurement

All participants underwent a scan of the lumbar spine (L1-L4) twice using a Hologic Horizon A DXA machine (Figure 1). Apex Software version 13.6.0.7 (Hologic, Inc., Bedford, MA, USA) was used for acquisition and analysis. To help ensure accurate measurements, participants were requested to change into hospital light clothing and to remove any metal or plastic artifacts that could potentially affect the BMD and TBS values. Following the first scan, participants were instructed to stand up and walk around the room for approximately 10-15 minutes before the second scan to help ensure that the measurements closely reflected actual conditions. The positioning of participants during the scans adhered to the manufacturer's recommended guidelines (12). After image acquisition, the lumbar spine image underwent analysis by

Table 1. Demographic data of participants (n=30)

	Mean ± SD	Range
Age (yrs)	58.8±4.0	56.0-67.0
Height (cm)	155.0±5.2	158.0-167.0
Weight (kg)	57.4±8.6	59.8-80.0
BMI (kg/m^2)	23.9±3.6	16.8-32.0

placing the ROI at L1-L4 to compute the BMD value (Figure 2). The same lumbar spine image ROI were employed to calculate the TBS values for various combinations of vertebrae using TBS insight software version 3.0.2.0 (Medimaps, Geneva, Switzerland) (Figure 3). All measurements were conducted using the same scanning mode (fast array), positioned and analyzed by same technologist, a ISCD-certified technologist with over 10 years' experience in DXA, and passed the precision test to avoid variation between measurements. A daily quality control test was conducted prior to scanning and consistently met the required standards. A spine phantom was scanned 10 times daily without repositioning, and the variation in BMD, BMC, and area values remained within 0.2%. No significant drift or shift in calibration was observed throughout the study period, which encompassed all participant measurements.

Statistical analysis

Descriptive statistics, including mean ± standard deviation (SD), were calculated using Microsoft Excel 2019 for all participant data.

Determination of precision error of BMD and TBS equivalent to the root mean square standard deviation (RMS-SD) or percent coefficient of variation (CV%), was performed using equations (1) and (2), respectively (13). The LSC of BMD and TBS were determined at a 95% confidence level using RMS-SD and (%CV) as 2.77 times of the precision, represented in equation (3). Precision error and LSC were computed using the ISCD Advanced Precision Calculation Tool (14). The levels of LSC

Figure 1. Positioning of lumbar spine scan by DXA

of BMD and TBS were considered acceptable with a %CV of ≤ 5.3% and ≤ 5.8%, respectively (3, 15).

$$RMS\ SD = \sqrt{\frac{\sum_{i=1}^{m}(SD_i)^2}{m}} \quad (1)$$

Where: m = number of subjects
SD = standard deviation

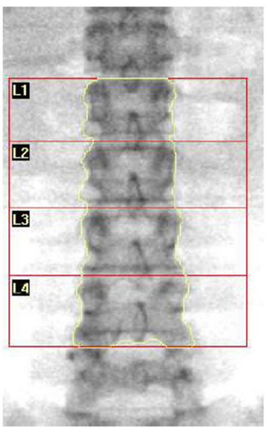
$$RMS\ \%CV = \sqrt{\frac{\sum_{i=1}^{m}(CV_i)^2}{m}} \times 100 \quad (2)$$

Where: m = number of subjects
CV = coefficient of variation

LSC=2.77 (precision error) (3)

RESULTS

The descriptive results for lumbar spine BMD and TBS in different vertebrae combinations are given in Table 2, while Table 3 presents the precision values for lumbar spine BMD and TBS across different vertebrae combinations.



Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	Z-score
L1	12.86	11.67	0.907	-0.5	1.0
L2	14.23	12.79	0.899	-0.7	1.0
L3	15.63	14.24	0.911	-1.0	0.8
L4	18.34	16.17	0.882	-1.2	0.8
L1-L2	27.08	24.45	0.903	-0.3	1.3
L1,L3	28.48	25.91	0.910	-0.5	1.2
L1,L4	31.19	27.83	0.892	-0.9	0.9
L2-L3	29.85	27.03	0.905	-0.9	0.9
L2,L4	32.56	28.95	0.889	-1.2	0.7
L3-L4	33.97	30.41	0.895	-1.4	0.6
L1-L3	42.71	38.70	0.906	-0.6	1.1
L1-L2,L4	45.42	40.62	0.894	-0.8	1.0
L1,L3-L4	46.82	42.08	0.899	-0.9	0.9
L2-L4	48.19	43.20	0.896	-1.2	0.7
L1-L4	61.05	54.87	0.899	-0.9	0.9

Figure 2. An example of analysis and results of BMD of vertebrae combinations

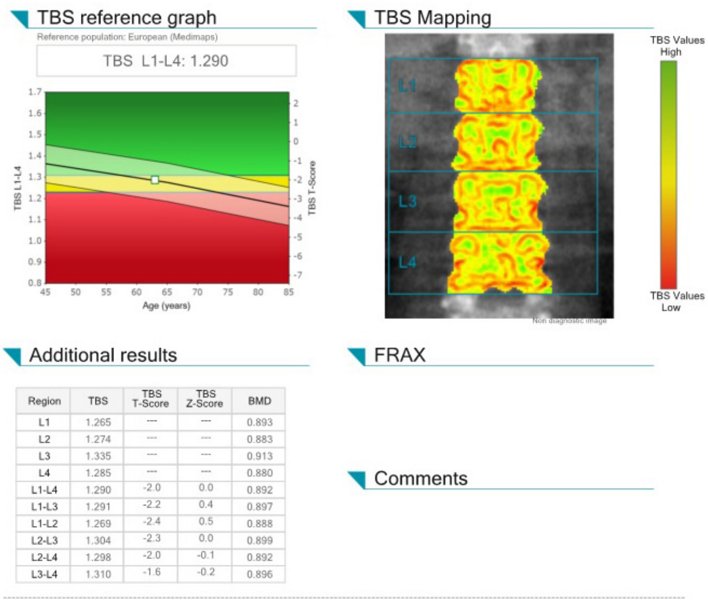


Figure 3. An example of analysis and results of TBS vertebrae combinations

The precision and LSC for 4 vertebrae combinations showed smallest value. The combination of 3 and 2 vertebrae exhibited larger values than the 4 vertebrae combinations, and individual vertebra demonstrating the greatest values. None of the lumbar spine vertebrae combinations exceeded acceptable levels (LSC value of BMD and TBS were within 5.3% and 5.8%, respectively), except individual vertebra combinations of TBS, which exhibited significantly lower precision.

DISCUSSION

Precision and LSC function as vital clinical tools for determining the minimum change in DXA serial measurements which can be considered a statistically significant change. Computation of precision and LSC at each DXA facility, as recommended by the ISCD, assists physicians in report interpretation and facilitates monitoring of response to treatment and disease progression (16).

In this study, we determined the precision and LSC for BMD and TBS in the lumbar spine, by considering both individual vertebra and various combinations of vertebrae of volunteer participants aged between 56 and 67. The age and physical condition of the participants was representative of the patient population undergoing BMD measurement in our department and followed the ISCD recommendations for BMD measurement (17). The determination of precision and LSC for BMD and TBS in younger participants may not be a good representative because the reproducibility of BMD measurements in younger patients might be higher due to more ease in repositioning than elderly participants (18).

Table 2. Mean and SD of lumbar spine BMD and TBS in different vertebrae combinations

Vertebrae combinations of lumbar spine (L1-L4)	Mean±SD	
	BMD	TBS
L1L2L3L4	0.857±0.158	1.359±0.068
L1L2L3	0.846±0.152	1.353±0.075
L2L3L4	0.871±0.164	1.375±0.710
L1L2L4	0.845±0.157	1.346±0.069
L1L3L4	0.862±0.161	1.349±0.067
L1L2	0.821±0.150	1.337±0.078
L1L3	0.850±0.153	1.344±0.075
L1L4	0.850±0.163	1.335±0.069
L2L3	0.864±0.156	1.378±0.082
L2L4	0.863±0.166	1.369±0.071
L3L4	0.886±0.173	1.376±0.074
L1	0.805±0.153	1.301±0.085
L2	0.838±0.153	1.373±0.082
L3	0.888±0.163	1.386±0.094
L4	0.884±0.187	1.366±0.085

BMD, bone mineral density; TBS: trabecular bone score; SD, standard deviation

The precision of the BMD 4 vertebrae combination showed the greatest precision (%CV = 0.62). The precision trend was declined for the 3 vertebrae combination (%CV range 0.65-0.81), the 2 vertebrae combination (%CV range 0.75-1.03), and individual vertebra (%CV range 0.94-1.32). The LSC of BMD with the 4 vertebrae combination (%CV = 1.71), the 3 vertebrae combination (%CV range 1.86-2.24), the 2 vertebrae combination

Table 3. Lumbar spine precision and LSC of BMD and TBS in different vertebrae combinations

Vertebrae combinations of lumbar spine (L1-L4)	Precision				LSC			
	BMD		TBS		BMD		TBS	
	RMS-SD	%CV	RMS-SD	%CV	RMS-SD	%CV	RMS-SD	%CV
L1L2L3L4	0.005	0.62	0.017	1.22	0.013	1.71	0.046	3.38
L1L2L3	0.006	0.81	0.210	1.56	0.018	2.24	0.059	4.31
L2L3L4	0.005	0.67	0.021	1.55	0.015	1.86	0.057	4.28
L1L2L4	0.005	0.65	0.019	1.43	0.014	1.79	0.053	3.96
L1L3L4	0.006	0.68	0.018	1.31	0.015	1.87	0.049	3.62
L1L2	0.007	0.93	0.024	1.81	0.020	2.59	0.067	5.00
L1L3	0.008	0.97	0.025	1.81	0.022	2.69	0.069	5.03
L1L4	0.006	0.78	0.024	1.85	0.017	2.15	0.066	5.11
L2L3	0.008	1.03	0.029	2.13	0.022	2.86	0.080	5.61
L2L4	0.006	0.75	0.023	1.73	0.017	2.08	0.064	4.78
L3L4	0.006	0.77	0.021	1.54	0.017	2.12	0.058	4.27
L1	0.012	1.44	0.041	3.24	0.032	3.54	0.114	8.98
L2	0.009	1.11	0.036	2.70	0.024	4.00	0.100	7.48
L3	0.011	1.32	0.034	2.49	0.030	3.67	0.094	6.91
L4	0.008	0.94	0.030	2.23	0.021	2.60	0.084	6.17

BMD, bone mineral density; TBS, trabecular bone score; RMS SD, root-mean-square deviation; %CV, % coefficient of variation; LSC, least significant change

(%CV range 2.08-2.86), and the individual vertebra (%CV range 2.60-4.00) are shown in Table 3. Nevertheless, none of the %CV values for BMD in any of the combinations exceeded 5.3%, the maximum level recommended by ISCD (17). Comparing the precision and LSC of RMS-SD and the %CV for BMD in our study with those of previous studies by Whittaker et al. (19), McNamara et al. (20), and Hind and Oldroyd (10), found noteworthy similarities.

For TBS, the precision and LSC followed a similar pattern to those of BMD. However, the precision and LSC of TBS were inferior to those of BMD. Moreover, the LSC of an individual vertebra was unacceptable (%CV range 6.17-8.98 (Table 3), while the threshold recognized by ISCD for monitoring TBS changes is %CV=5.8) (15).

Our findings indicate that all combinations of vertebrae can be utilized for monitoring changes in BMD. However, to gain further insights beyond BMD and bone turnover markers, it is advisable to monitor changes in TBS, specifically in 2-4 vertebrae combinations, but not in individual vertebra. This recommendation is particularly relevant for patients undergoing anabolic therapy (teriparatide and abaloparatide).

It is essential to also acknowledge the limitations of this study. First, all participants in this study were females. Although the ISCD does not offer specific recommendations regarding gender-based precision studies (11) and Krueger et al. found no significant difference in BMD precision between females and males (21), further study of precision and LSC for lumbar spine BMD and TBS in male populations are necessary. Additionally, it should be noted that the results of this study were obtained using specific manufacturers and models of DXA machines (Hologic, Horizon A) and thus may not be generalizable to all manufacturers and models. Finally, all participants enrolled in this study were staff of our hospital, not patients. The precision and LSC values of BMD and TBS of our staff may be superior to those of general patients.

CONCLUSIONS

All vertebrae combinations can provide an acceptable level of precision and LSC for BMD monitoring. However, the precision and LSC of TBS are inferior to those of BMD, and individual vertebra are not appropriate for use in TBS monitoring.

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None

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Original Article **Open Access**

After-action Review of Hospital Environments Exploring the 'New Normal,' Focusing on Structural Management Aspects and Bacterial Culture in Thai Hospitals Amid the COVID-19 Pandemic

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ABSTRACT

OBJECTIVE This study aimed to explore the management of hospital environments during the COVID-19 pandemic, focusing on the structural aspects of 'new normal' health services delivery practices and bacterial culture in hospital rooms.

METHODS This study employed a cross-sectional design that involved the evaluation of hospital environment management, the detection of indoor bacterial colonies in hospitals, and interviews with healthcare administrators on the 'new normal' measures.

RESULTS The evaluation form was completed by 543 healthcare division heads from 30 hospitals. Respondents in each group reported that hospitals where they worked had effectively implemented new normal measures, making changes to the structure, processes, and personnel management components in line with the 'new normal' concept. The majority of the hospitals investigated, accounting for 71.7%, were found to have pathogenic bacterial counts lower than the permissible limits. The statistical analysis identified a significant association between ventilation, structural management under the 'new normal', and bacterial counts ($p < 0.05$).

CONCLUSIONS The incorporation of the structural aspects of new normal practices for managing the workplace environment should be a routine and integral part of efforts to control healthcare-associated infections in hospitals.

KEYWORDS hospital environment, the new normal, COVID-19, bacterial culture

INTRODUCTION

The COVID-19 pandemic is an important event affecting most of mankind. The COVID virus can evolve into other new variants. The incubation period of the virus is about 6.6 days after an individual is infected (1). Transmission of COVID-19 between people occurs primarily through respiratory droplets, known as droplet spread. Laboratory studies have found that the droplets can remain suspended in the air and continue to be infectious for up to 16 hours (2). The virus can also be transmitted through contact with contaminated surfaces (3). Environmental factors such as ventilation, temperature, humidity, and airborne infection isolation rooms can dilute and remove pathogens (4) which can reduce the risk of infection if these conditions are managed appropriately (4, 5). To control the transmission of the disease, the Thai government has implemented measures to prevent and control its spread throughout the country. Individual preventive measures, encompassing 'D' for distancing from social interactions, 'M' for mask-wearing, and 'H' for hand washing, were the primary preventative measures prior to the availability of COVID-19 vaccines in February 2021 (6-8). The WHO also recommends the implementation of protective measures for health workers (6). The rapid increase in COVID-19 cases during the pandemic also represents a heightened risk for healthcare workers, intensifying the challenges in the battle against COVID-19 (9, 10). Healthcare workers are at a higher risk of infection than the general population due to their close contact with colleagues, fellow workers, and family members who may already be infected by the virus (9, 10). Additionally, their occupational exposure to patients, particularly while performing medical procedures which involve potential exposure to droplets, further heightens the risk (9). As a consequence, healthcare workers can potentially contribute to a high rate of COVID-19 transmission. The prevalence of COVID-19 among healthcare workers was found to be 11% in Italy and 20% in England (10). In China, 1,716 healthcare workers were infected in the early stages of the epidemic (9). As a consequence, setting up measures to prevent the spread of infectious microbes in hospital areas became an urgent priority for virtually all healthcare facilities in response to COVID-19. As part of the immediate response to the pandemic, the Thai healthcare community considered adopting a 'new normal' medical service system, which involves changing or adapting various components of hospital environments and facilities in the areas of structure, process, and personnel (11). The 'new normal' healthcare services management adopted has demonstrated its effectiveness, aligning with the concept of providing healing environments and prioritizing environmental quality for healthcare buildings. This approach creates pleasant, functional, and comfortable spaces (12, 13), and serves as a crucial measure for preventing hospital staff from contracting contagious diseases. The term 'new normal,' widely used during the COVID-19 event, refers to the altered state of affairs or lifestyle that emerges following an unfamiliar experience, situation, or sudden crisis, ultimately evolving into new standards and typical practices (14). In healthcare facilities in Thailand, the new normal is evident in structural changes such as the installation of wall dividers for separated spaces and improvements to ventilation systems. Additionally, there have been modifications to screening methods, communications, and measures to ensure the well-being of hospital personnel, all in response to the surge in COVID-19 cases and hospital patients. Importantly, the new normal healthcare system can serve as a lasting mechanism which can continue to operate even after COVID-19 subsides, helping to prevent the spread of infections and diseases caused by other contagious pathogens present in hospital areas (15).

The present study, conducted following the first wave of COVID-19 in Thailand, serves as an exploration of the environmental management measures implemented by Thai healthcare facilities within the new normal framework. Additionally, the study investigated bacteria cultures in hospitals to identify contamination, aiding preparedness in the ongoing fight against the epidemic. The findings lead to the proposal to apply the new normal healthcare services delivery system used during the COVID-19 crisis as a preventive measure against future healthcare-associated infections. This initiative aims to enhance safety and health concerns for both personnel and patients.

METHODS

This investigation employed a cross-sectional design involving provincial hospitals, general hospitals, community hospitals, and private hospitals in the Bangkok metropolitan area as well as the Central and Eastern regions of Thailand. The research received approval from the Ethics Committee at Nopparat Rajathanee Hospital, with funding support provided by the Thailand Science Research and Innovation (TSRI).

The participating hospitals were identified by purposive sampling and the sample included 543 healthcare division heads from 30 healthcare facilities which consented to participate in the research. The necessary data and information were collected between April and December 2021 which was after the first wave of COVID-19 had come to an end. The investigation was undertaken in three parts employing different study tools as follows.

1. The evaluation of the use of new normal measures to prevent the spread of COVID-19

incorporated guidance from Guidance on Preparing Workplaces for COVID-19 and the COVID-19 Healthcare Planning Checklist (16). The evaluation covered three aspects of the new normal, with 11 questions on physical structure aspects, 16 questions on process management aspects, and 15 questions on personnel aspects, plus 4 questions related to policies. Responses were categorized into three levels: 0 for 'no,' 1 for 'yes but not comprehensive coverage,' and 2 for 'yes, covering the entire hospital'. An evaluation form was developed and reviewed by three experts. The evaluation form then underwent reliability test using the Cronbach's alpha method. That test yielded a calculated alpha coefficient value of 0.75. Subsequently, the form was distributed to 550 personnel division heads for online evaluation.

2. Inspection of air quality and bacterial culture tests were conducted in 150 hospital rooms across 15 healthcare facilities, covering various spaces including offices, examination rooms, and hospital wards. The equipment used included the universal Indoor Air Quality (IAQ) measurement following the ASHRAE 55 Standard (17). Air samples were collected using suction, and assessments of bacterial cultures were conducted according to the NIOSH method number 0800 standard (18).

3. Structured interviews were conducted with hospital administrators holding positions such as director, deputy director, member of the occupational health team, and member of contagious disease control and prevention teams. The interviews used a questionnaire containing items related to policies and structural organization, the arrangement of the healthcare provision system for COVID-19-infected patients, healthcare workers and professionals, and information on the implementation of measures to protect healthcare personnel and transitioning towards new normal practices.

Statistical analysis

The data processing and analysis used the Statistical Package for the Social Sciences to calculate frequencies and arithmetic means. Relationships between scores of the new normal management and the bacteria colonies groups were explored using odds ratio (OR) along with their 95% confidence intervals (95% CIs), with a $p < 0.05$ considered statistically significant. The data analysis employed the Generalized Linear Model (GLM) which can address confounding effects from factors such as room type, cleaning procedures, air movement, air temperature, relative humidity, CO, and CO_2.

RESULTS

The study found an average score of 16.3 (out of 20) for hospitals implementing the structural aspect management of the new normal measures. Implementation primarily took the form of setting up isolation rooms for COVID-19-infected patients in both ARI clinics and cohort wards, designating a room for swab collection, optimizing open-air spaces, improving ventilation systems, and other measures as detailed in Table 1.

Table 1. Scores for implementing 'new normal' structural management measures

Structural Management	Score		
	0	1	2
1. Provide isolated areas for suspected infectious groups	9 (1.7)	129 (23.8)	405 (74.6)
2. Provide adequate hand sanitizer	2 (0.4)	79 (14.5)	462 (85.1)
3. Support in providing rooms for cohort wards	21 (3.9)	89 (16.4)	433 (79.7)
4. Support in providing rooms for swabs	46 (8.5)	131 (24.1)	366 (67.4)
5. Limiting access in hospital buildings	7 (1.3)	163 (30.0)	373 (68.7)
6. Promoting space distancing between persons in hospital (waiting rooms and cafeterias)	42 (7.7)	149 (27.4)	352 (64.8)
7. Partitioning areas	6 (1.1)	135 (24.9)	402 (74.0)
8. Setting areas for isolation and quarantine of high-risk personnel	33 (6.1)	121 (22.3)	389 (1.6)
9. Improving ventilation in the hospital	16 (2.9)	172 (31.7)	355 (65.4)
10. Separate accommodation facilities for COVID team members	94 (17.3)	170 (31.3)	279 (1.4)
11. Separate bathing and clothes changing areas for COVID team members	30 (5.5)	131 (24.1)	382 (70.3)

0, no; 1, yes but not comprehensive coverage; 2, yes, covering the entire hospital

The study also calculated a score of 28.9 (out of 34) for the new normal measures in the area of process management, which included the establishment of an ad hoc committee to review policy development, and the determination to develop a healthcare management system for COVID-19-infected patients. This new normal system involved screening of symptomatic patients, maintaining patient medical records, and providing telemedicine delivery services to reduce hospital congestion. A score of 25.3 (out of 30) was achieved for the personnel aspects, encompassing the provision of knowledge and guidelines for healthcare workers (HCWs) dealing with COVID-19 patients to prevent virus spread and for protection against the disease. Support for the use of personal protective equipment (PPE), the designation of isolated working areas, and the monitoring of the safety and well-being of HCWs with high-risk exposure to COVID-19 were also included. In essence, the various new normal measures were assessed to be crucial contributors to controlling the spread of COVID-19, consistent with the results obtained from interviews with hospital administrators.

The culture test of bacteria in the indoor environment of a total of 150 rooms across 15 hospitals was compared with general data, ventilation data, and new normal data, covering those three aspects. The results revealed that in the majority of areas (70%), total bacterial counts were within acceptable limits, as detailed in Table 2. To account for confounding effects, a statistical test evaluated the relationship between various factors among groups with total bacterial counts exceeding acceptable levels as detailed in Table 3. Interestingly, the office and OPD/Ward areas demonstrated the strongest association with exceeding acceptable total bacterial counts (AOR 76.1; 95% CI: 4.0-1,449.3 and AOR 18.9; 95% CI: 1.4-259.0) (Table 2). An increase of 1 unit in air movement correlated with a decrease of approximately 38% in total bacterial counts for groups that exceeded acceptable levels (95% CI: 0.4-0.9). Additionally, relative humidity and carbon monoxide (CO) gas were associated with groups exceeding acceptable bacterial counts (AOR 1.1, 3.0; 95% CI: 1.01-1.2, 1.2-7.5, respectively). Moreover, higher scores on structural aspects were associated with a decrease in groups with unacceptable total bacterial counts (AOR 0.56; 95% CI: 0.34-0.92)."

Through interviews with hospital administrators at 30 locations, it was found that they deemed certain 'new normal' practices, outlined in Table 4, as suitable for continued and routine use. These practices, especially those aimed at reducing the spread of infectious microorganisms in the hospital environment, include the establishment of an isolated acute respiratory infection (ARI) clinic, improvement of ventilation systems, development of a screening system for acute respiratory infection symptoms, utilization of telemedicine technology to alleviate hospital congestion, and the implementation of a wellness system for the healthcare workforce to protect healthcare workers from virus infections and from becoming vectors of disease transmission.

DISCUSSION

The research findings reveal that the management of hospital environments, particularly physical structure components, included in the new normal measures, is highly effective. The mean

Table 2. The relationship between bacterial colony and hospital factors

Hospital factors	Bacterial colony (SD)	*p*-value	Hospital factors	Bacterial colony (SD)	*p*-value
Room type		0.01	Frequency of cleaning		0.14
Clean (50)	119.4 (141.5)		1 time/day (38)	216.7 (141.5)	
Ward/OPD (83)	275.4 (275.6)		2 time/day (102)	294.0 (275.6)	
Office (15)	429.3 (313.4)				
Structural management		0.35	System management		0.99
≤ 80% (35)	313.0 (306.9)		≤ 80% (45)	273.9 (287.6)	
> 80% (115)	262.7 (267.2)		> 80% (105)	274.6 (273.3)	
Staff management		0.87			
≤ 80% (65)	270.0 (257.5)				
> 80% (85)	277.8 (292.0)				

Table 3. Odds ratios (OR) of exceeding permissible bacteria counts and their 95% confidence intervals for each variable adjusted for all other factors using GLMs

Variable	N (%)	SE	OR	AOR	95% CI		*p*-value
					Lower	Upper	
Office	15 (10.1)	1.5035	32.667	76.099	3.996	1,449.347	< 0.01
OPD/Ward	83 (56.1)	1.3360	11.701	18.884	1.377	258.992	< 0.05
Clean room	50 (33.8)		1.000	1.000			
Cleaning: 1 time/day	38 (25.7)	0.7112	0.563	0.696	0.173	2.805	> 0.05
Cleaning: 2 times/day	110 (74.3)		1.000	1.000			
Air movement	148 (100.0)	0.2089	0.894	0.619	0.411	0.932	< 0.05
Air Temperature	148 (100.0)	0.1978	1.214	1.200	0.814	1.769	> 0.05
Relative humidity	148 (100.0)	0.0417	1.033	1.098	1.012	1.192	< 0.05
Carbon monoxide (CO)	148 (100.0)	0.4633	1.628	3.026	1.220	7.502	< 0.05
Carbon dioxide (CO_2)	148 (100.0)	0.0018	1.004	1.006	1.003	1.010	< 0.01
System management score	148 (100.0)	0.3106	1.057	1.555	0.846	2.858	> 0.05
Structural management score	148 (100.0)	0.2512	0.927	0.559	0.342	0.915	< 0.05

Adjust for room type, cleaning, air movement, air temperature, relative humidity, CO, CO_2, system management score, structural management score

Table 4. The 'new normal' measures to prevent the spread of infection which are normally practiced in 30 hospitals

Measures to prevent the spread of infection	Percent
• Restructured hospital administration and management systems to fight against new and re-emerging diseases	90.9
• Set up an ARI clinic as a medical examination room outside the main hospital buildings	18.2
• Adjusted the ventilation system throughout the hospital to better care for infected patients	100.0
• Set up and/or added AIIR rooms for isolating patients with contagious respiratory infections	27.3
• Organized a screening system to be used before conducting some important services, e.g., surgery and obstetrics	100.0
• Use Telemedicine and other online services to reduce hospital congestion	18.2
• Providing occupational health services to help prevent infection of healthcare personnel	100.0
• Provided training on how to care for infected patients, PPE use and universal precautionary measures	100.0

score of 16.3 out of 20, while the lowest among the new normal aspects, indicates that most hospitals have dedicated efforts and resources to manage hospital environments comprehensively. This includes not only the physical structure component but also the linkages and relationships among various parts of healthcare facilities. Even though a hospital operates as an organization with many self-contained departments or work units, it must also function as a complex adaptive system (19) which can effectively respond to the rapidly increasing demand for healthcare services with the new normal setting. This new normal endeavor represents a comprehensive concept of managing hospital facilities and environments, encompassing the components of people, places, and processes (20). According to the present study, the majority of hospitals were found to have implemented changes to various elements of the structural component, particularly the management or establishment of ARI clinics, cohort wards, and swab collection rooms, at 98.3%, 79.0%, and 54.0%, respectively. These changes are aimed at isolating suspected or confirmed COVID-19 cases from the main hospital buildings and/or confining them to designated places. The implementation of physical isolation methods (4, 21) to restrict the presence of COVID-19-infected patients to certain areas within the hospital premises is a practical measure to minimize pathogen contamination in other hospital areas. This study observed that all hospitals had restructured their screening procedures in ARI clinics to expedite initial diagnosis, serving as a preventive measure for contagious disease control and the spread of COVID-19 to healthcare personnel and patients (21). Notably, 98.4% of the hospitals in this study set up ARI clinics outside the main hospital buildings to maximize outdoor air flow and solar radiation (22), thereby isolating ARI patients. Although the use of open-air space for routine ARI clinic services during normal times might result in some level of discomfort for both service users and healthcare personnel. Interviews with hospital administrators also revealed that 68.2% had considered improving the ventilation system to generate negative pressure in hospital rooms. This measure is aimed at preventing airborne contaminants from COVID-19 patients in one room from flowing out into the surrounding area.

These changes align with CDC recommendations advocating for the use of negative pressure rooms and respirators with HEPA filters to accommodate confirmed COVID-19 patients in healthcare facilities. The establishment of negative pressure rooms for swab collection to confirm viral infections also conforms with these guidelines (4, 21). Regarding physical distancing measures, 22.7% of hospitals utilized fixed or movable partitions or room dividers, while the majority, 92.2%, promoted the use of face shields. This approach aims to reduce the transmission risk of the virus from COVID-19 patients to healthcare personnel engaged in activities with close contact (within one meter) (21) and exposure times longer than 15 minutes (23). Hospitals also implemented various strategies for physical distancing, including widening the space between seats in waiting rooms, providing remote clinical and non-clinical services through online communication technologies like telehealth and telemedicine, sending prescribed medicines via post, and enforcing a no visitation policy. These arrangements collectively contributed to lowering the number of patients visiting the hospital and reducing hospital congestion (24).

Protecting the health and safety of healthcare personnel, especially those providing care to COVID-19 patients and those facing high exposure risks, is paramount to reducing hospital-acquired virus dispersion. Some healthcare facilities have established special COVID response teams dedicated to handling COVID-19 patient care. These teams are provided with housing accommodations that allow isolation from other individuals, including their families, and undergo rigorous health monitoring before returning to their respective work units or offices. The protocols for these COVID response teams mirror those applied to other healthcare professionals with high exposure risk (25, 26) which aim to minimize healthcare-associated infections among medical staff. This proactive approach helps mitigate the risk of staff shortages and helps ensure the continuous provision of services to patients. The majority of hospitals in this study have designated specific shower rooms and clothes changing areas exclusively for the use of personnel caring for COVID-19 patients. This strategic arrangement aims to diminish the likelihood of these healthcare workers becoming vectors of virus transmission to their colleagues, patients, and family members, thereby contributing to the prevention and control of virus spread (27).

Environmental quality also plays a crucial role in reducing contamination and preventing the spread of pathogens in hospitals (28), thereby preventing hospital outbreaks. This study conducted laboratory tests of air-borne pathogenic bacteria using culture techniques, revealing that in the majority of hospitals studied (71%), the number of bacterial colonies did not exceed the permissible limit. Factors found to be associated with exceeding acceptable bacteria counts included lower air movement, higher humidity, and higher CO_2 levels. Notably, carbon monoxide (CO) was found to triple the risk of exceeding acceptable bacteria counts. When the scores for the structural aspects of the new normal were equal to or exceeded 80%, there was a 44.1% decrease in the risk of exceeding permissible bacteria counts ($p < 0.05$). Furthermore, no relationship was detected between indoor bacterial colonies and air changes per hour. This finding aligns with the results of a study by Memarzadeh, which suggests that the critical factor in the spread of bacterial droplet contamination is the path between the contaminant source and the exhaust system rather than the ventilation airflow rate (29). Through interviews with hospital administrators, it was confirmed that adjustments in structural practices are being made for continued and routine use in an effort to reduce the spread of infectious microorganisms in the hospital environment. These strategic changes have been recommended as a preparation for the potential next wave of the pandemic.

This study has a few limitations. First, the questionnaire on the ‘new normal’ was not derived directly from guidelines, but was adjusted based on practices during the pandemic situation. Additionally, the bacteria culture analyses were conducted in only 15 hospitals, as this study commenced during the onset of the second wave of the pandemic.

Modification of the management of hospital environments and facilities in response to COVID-19 should be a top priority. Implementing structural measures, such as the establishment of isolation rooms and improvement of ventilation systems, is crucial for effectively reducing the spread of contagious agents in the hospital environment. Implementation of these actions, in addition to the re-arrangement of healthcare service provision and delivery systems and the establishment of measures to protect healthcare personnel in accordance with the 'New Normal' medical services policy of the Thai Ministry of Public Health, has indeed proven to be effective in curbing healthcare-associated COVID-19 infections. Thus, the new normal practices should continue to be adopted and/or adapted as guidelines for use in times of normality to control the occurrence of future healthcare-associated infections and disease spread which represent a major risk to healthcare, business and industry.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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Differences in the Characteristics and Factors Associated with Insulin Resistance in Normal Weight and Overweight Polycystic Ovary Syndrome Women

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ABSTRACT

OBJECTIVE This research aimed to compare clinical and biochemical parameters between normal and overweight-obese polycystic ovary syndrome (PCOS) patients, and to determine the association between insulin resistance (HOMA-IR) and anthropometric, biochemical and hormonal factors in both groups of PCOS.

METHODS This study was of a cross sectional design. PCOS was diagnosed using the Revised Rotterdam Criteria 2003. Participants underwent history taking and physical examination. Blood samples were collected for FPG, insulin, lipid profiles, TSH, FSH, LH, SHBG, total testosterone, and free androgen index (FAI). Insulin resistance index was calculated by homeostatic model assessment (HOMA-IR). Clinical and biochemical parameters were compared between both groups of PCOS. Associations between HOMA-IR and anthropometry, biochemistry and hormonal parameters between groups were determined separately.

RESULTS Sixty-four female with PCOS were enrolled. Comparison of biochemical analyses found that the free androgen index was higher and that LH and SHBG were lower in the overweight-obese group. HOMA-IR was greater in the overweight-obese group. In the overweight-obese group, there were statistically significant correlations between the HOMA-IR with the measured BMI, waist circumference, waist-height ratio, HDL, triglycerides, SHBG and the free androgen index. Interestingly, in the normal weight group, only the triglycerides, SHBG and the free androgen indix had a statistically significant correlation with HOMA-IR.

CONCLUSIONS There were clear differences in the parameters related to insulin resistance between overweight-obese and normal weight PCOS; however, triglycerides, SHBG, and the free androgen index played a significant role in insulin resistance in both groups of PCOS.

KEYWORDS homeostasis model assessment (HOMA-IR), insulin resistance, polycystic ovary syndrome

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INTRODUCTION

Over the past few decades, the way of life of the Thai population has undergone rapid changes. Urbanization, less physical activity and consuming a high calorie diet has led to an increasingly overweight and obese population which has also been noted in reproductive age females. Twenty percent of young Thai females have been found to exhibit class I obesity and 12.9% have class II obesity (1). Increased body weight often results in abnormal menstruation in adolescents and adults. PCOS is one of the leading causes of abnormal menstruation in adolescent and adult Thai females and closely correlates with infertility, obesity and diabetes (2). A study of 600 university students in Thailand reported that the prevalence of Polycystic Ovary Syndrome (PCOS) in Thai adolescents was 5.29% (3). In a study of 250 PCOS patients from Siriraj Hospital, Thailand it was found that 49% of the cases had central obesity which was correlated with insulin resistance, abnormal lipid metabolism, and increased male sex hormone production (4). In addition to the Oral Glucose Tolerance Test (OGTT), the insulin resistance in PCOS was also assessed by calculations using the Homeostatic Model Assessment–Insulin Resistance (HOMA–IR) (5, 6). A percentage of these patients progressed to development of diabetes mellitus (7).

Classical PCOS patients have irregular menstruation or amenorrhea together with increased body hair, especially on the lip and upper chest wall as well as increased skin sebaceous glands and acne. Insulin resistance in these patients can lead to hyperinsulinemia. Insulin resistance and hyperinsulinemia cause increased hepatic gluconeogenesis, increased glycogenolysis and can finally progress to diabetes (8). Current concepts of PCOS pathophysiology include functional ovarian hyperandrogenism (FOH) and functional adrenal hyperandrogenism (FAH), polycystic ovarian morphology, LH excess, insulin resistance with hyperinsulinism and obesity. Additionally, FOH plays a principal role in PCOS pathophysiologic abnormality in which increased hyperandrogenemia results in negative feedback on gonadotropin release resulting in excess LH (9). Because PCOS is found in both normal weight and overweight-obese women, many clinical studies have compared biochemical markers between obese and non-obese women with PCOS in order to understand the differences in pathophysiology of PCOS between obese and non-obese PCOS. A study in China found elevated of estradiol (E2) in obese PCOS women compared with non-obese PCOS individuals; however, there were no differences in lipid profile, LH, FSH, testosterone, prolactin, or anti-mullerian hormone (AMH) between the two PCOS groups (10). Additional studies were not able to identify differences in AMH or cardiac risk markers (CRP, ADMA, Hcy, PAI-1, VEGF) between obese and non-obese PCOS (11, 12). Because adiposity plays a role in PCOS, searching for certain adipokines, e.g., endotrophin, adiponectin, ghrelin, as a novel marker in PCOS has been undertaken. One study reported that endotrophin had an association with HOMA-IR, LH/FSH and total testosterone in PCOS (13).

Nevertheless, insulin resistance is the principal pathogenesis in PCOS and affects both obese and non-obese PCOS patients. Previous clinical studies have emphasized the impact of chronic low-grade inflammation on insulin resistance in PCOS (14). Elevation of inflammatory markers such as CRP, WBC concentration, and IL-18, MCP-1 concentration has been observed in PCOS compared with controls (15-18).

The purpose of this research was to identify differences between factors associated with insulin resistance in normal weight PCOS and overweight-obese PCOS women by comparing the associations of insulin resistance (HOMA–IR) with anthropometric, biochemical, and hormonal parameters in both groups of PCOS. This was the first study to compare the correlation of hormonal and biochemical parameters and insulin resistance between lean and overweight-obese adolescent PCOS patients in the Thai population.

METHODS

Study population

Sixty-four Polycystic ovary syndrome (PCOS) patients from the Obstetrics and Gynecology Department of the Medical Center Hospital, Mae Fah Luang University, Chiang Rai, Thailand, from January 2021 to December 2021 were enrolled. PCOS was diagnosed according to The Revised Rotterdam Criteria 2003 (19). Inclusion criteria consisted of amenorrhea/oligomenorrhea and polycystic ovarian morphology confirmed by ultrasonography in all participants done by one of two gynecologists or by having hirsutism/signs of hyperandrogenemia. Our participants were classified as either PCOS phenotype A or phenotype D. Exclusion criteria were women who had diabetes, took anti-cholesterol medications, corticosteroids, used oral contraception (within 3 months prior to enrollment), had used either injected or implanted contraception, had taken anti-psychotic medications or weight lowering agents or who had previous ovarian surgery. Additionally, patients who had features of hyperthyroidism, hypothyroidism, cushing syndrome, or galactorrhea were also excluded from the study.

The research protocol was approved by the ethical committee of Mae Fah Luang University (COA 183/2020).

Clinical, anthropometric and biochemical measurements

After explaining the study process to the participants and obtaining informed consent, the participants underwent history taking and physical examination. Blood pressure was measured in both arms using a digital sphygmomanometer after a 20-minute rest. The average value of the blood pressure readings was used. Following the American College of Cardiology, pre-hypertension was defined as systolic blood pressure 120-129 mmHg and diastolic blood pressure less than 80 mmHg (20). Height and weight were measured for calculation of BMI. BMI at or above 23 kg/m^2 was defined as overweight and BMI above 25 kg/m^2 was defined as obese. Waist circumference was measured by one of the trained nursing staff in centimeters using a measuring tape at the mid-level between the lateral costal margin and iliac crest at full expiration with the patient in the standing position. Waist-height ratio was then calculated.

Acanthosis nigricans present on the back of the neck, axilla, or groin was recorded. The Ferriman-Gallwey scale was used to assess body hair for evidence of hyperandrogenemia. After 12 hours of fasting, blood samples were collected between 8.00 A.M. and 9.00 A.M. to measure plasma glucose, insulin, lipid profiles, TSH, FSH, LH, total testosterone, free testosterone, and SHBG.

Impaired fasting glucose was defined as a fasting plasma glucose from 100 mg/dL to less than 126 mg/dL. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL. Metabolic syndrome was defined as agreed to by the International Diabetes Federation 2005, in which participants achieved 3 of 5 criteria including blood pressure ≥ 130/85 mmHg, waist circumference ≥ 80 cm, triglycerides ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL, and fasting plasma glucose ≥ 100 mg/dL.

Insulin resistant state (HOMA-IR) was determined by the formula:

$$\text{HOMA-IR} = \frac{\text{Glucose (mg/dL)} \times \text{Insulin } (\mu\text{U/mL})}{405}$$

The cut-off level of HOMA–IR > 2 was defined as insulin resistance (5).

Fasting plasma glucose, TSH, and lipid profiles were measured by photometry (Cobas C 501 analyzer series, Roche Laboratory, Indianapolis, USA). Insulin, FSH, LH, and SHBG were measured by electro-chemiluminescence assay. Free testosterone was calculated based on total testosterone, SHBG, and albumin. Free androgen index (FAI) was calculated using the formula:

$$\text{Total testosterone} = [(\text{nmol/L}) \div \text{SHBG (nmol/L)}] \times 100$$

Statistical analysis

Statistical analysis was performed using SPSS version 25. Data are presented as median and interquartile range. The Mann-Whitney U test was used for comparison of clinical and biochemical parameters, including HOMA–IR and free androgen index, between the normal weight and the overweight-obese group. Spearman correlation coefficient was used for assessment of correlation between HOMA–IR and anthropometric, biochemical, hormonal parameters in both the normal and overweight-obese groups.

RESULTS

There were 64 PCOS patients enrolled in this study (28 in the normal weight group and 36 in the overweight-obese group). In the overweight-obese group 13.9% showed pre-hypertension, 13.9% had impaired fasting glucose but none had diabetes. One of the twenty-eight cases (3.6%) in the normal weight group had metabolic syndrome, whereas eight of thirty-six cases (22.3%) in the overweight-obese group had metabolic syndrome (Table 1). Comparison of clinical features between the normal weight and the overweight-obese group found that systolic and diastolic blood pressure were higher in the overweight-obese group. The Ferriman-Gallwey scale was also higher in this group compared to the normal weight group (Table 2).

Regarding biochemical parameters, the overweight-obese group had higher fasting insulin levels and triglycerides and lower HDL-cholesterol levels compared to the normal weight group. Interestingly, the LH level in the normal weight was higher than in the overweight-obese (p = 0.03), but the FSH and LH/FSH ratio were not statistically significantly different. In addition, the free androgen index was higher in the overweight-obese group, which is compatible to the higher hirsutism found using the Ferriman-Gallwey scale. SHBG, as expected, was lower in the overweight-obese group ($p < 0.001$). Regarding insulin

Table 1. Prevalence of pre-hypertensive state, impaired fasting glucose, diabetes, metabolic syndrome and insulin resistance in study participants (n = 64)

	BMI < 23 kg/m^2 n = 28	**BMI ≥ 23 kg/m^2 n = 36**
Pre-hypertension	0 (0.0%)	5 (13.9%)
Impaired fasting glucose	0 (0.0%)	5 (13.9%)
Diabetes mellitus	0 (0.0%)	0 (0.0%)
Metabolic syndrome	1 (3.6%)	8 (22.3%)
Insulin resistance (HOMA-IR > 2)	2 (7.1%)	23 (64.9%)

BMI, body mass index; pre-hypertension, systolic blood pressure 120-129 mmHg and diastolic blood pressure less than 80 mmHg

Table 2. Comparison of anthropometric and laboratory parameters between BMI < 23 kg/m^2 with BMI ≥ 23 kg/m^2 (expressed as median and IQR with Mann-Whitney U test) $p < 0.05$

	BMI < 23 kg/m^2 n = 28	**BMI ≥ 23 kg/m^2 n = 36**	***p*-value**
Age	24.00 (20.30-28.00)	22.00 (22.00-27.80)	0.749
Systolic blood pressure (mmHg)	110.00 (102.00-110.00)	120.00 (112.00-125.00)	< 0.001*
Diastolic blood pressure (mmHg)	70.00 (70.00 – 80.00)	80.00 (70.00 – 80.00)	< 0.001*
Height (cm)	158.30 (153.30-163.80)	159.00 (153.50-163.00)	0.082
Weight (kg)	52.10 (48.00-56.40)	74.80 (66.70-89.00)	< 0.001*
BMI (kg/m^2)	20.90 (19.70-21.90)	30.20 (25.80-34.40)	< 0.001*
Waist circumference (cm)	67.50 (63.90-71.50)	88.00 (79.40-97.30)	< 0.001*
Waist–height ratio	0.42 (0.41-0.44)	0.56 (0.49-0.61)	< 0.001*
Ferriman- Gallwey scale	6.00 (3.00- 9.70)	10.50 (5.30-16.80)	0.005*
Fasting plasma glucose (mg/dL)	86.00 (82.00-89.00)	87.00 (82.00-94.00)	0.238
Insulin (μU/mL)	5.20 (3.50-6.30)	13.40 (7.60-20.20)	< 0.001*
HOMA-IR	1.10 (0.70-1.50)	2.90 (1.60-4.30)	< 0.001*
Glucose insulin ratio (mg/dL)/(μU/mL)	16.80 (14.00-24.50)	6.50 (4.50-11.70)	< 0.001*
FAI	3.00 (1.90-5.80)	9.70 (5.50-14.60)	< 0.001*
Free testosterone (ng/dL)	0.57 (0.40-0.89)	1.09 (0.80-1.50)	< 0.001*
SHBG (nmol/L)	48.10 (30.76-70.00)	18.40 (13.73-27.52)	< 0.001*
LH (mIU/mL)	7.69 (5.30-13.64)	6.77 (4.15-8.52)	0.030*
FSH (mIU/mL)	5.34 (3.88-6.73)	4.98 (4.01-5.77)	0.310
LH/FSH ratio	1.60 (1.10-2.20)	1.40 (1.10-1.70)	0.170
Cholesterol (mg/dL)	193.00 (177.00-222.00)	192.00 (180.00-221.00)	0.756
Triglycerides (mg/dL)	79.00 (57.00-103.00)	121.00 (78.00-167.00)	< 0.001*
HDL - C (mg/dL)	65.00 (56.00-74.00)	46.00 (40.00-53.00)	< 0.001*
LDL – C (mg/dL)	110.00 (100.00-143.00)	119.00 (105.00-137.00)	0.593
TSH (μIU/mL)	1.58 (1.35-2.28)	1.90 (1.45-2.91)	0.077

BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FAI, free androgen index; FSH, follicular stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone resistance, HOMA-IR was significantly higher in the overweight-obese group than in the normal weight group (2.9 compared with 1.1), despite of having the same level of fasting plasma glucose (Table 2).

Correlations among BMI, waist circumference and waist-height ratio in the overweight-obese group showed indications that insulin resistance was related to possessing higher body fat. Analysis of the association between insulin resistance state (HOMA-IR) with anthropometric measurements revealed strong associations between weight, BMI, waist circumference, waist-height ratio and HOMA-IR in the overweight-obese group (Table 3). However, this study found no association between these parameters and HOMA-IR in the normal BMI group (Table 4).

Lipid profiles, both triglycerides and HDL cholesterol, were associated with HOMA-IR in overweight-obese individuals. Importantly, triglycerides, free androgen index and SHBG had a strong association with HOMA-IR in both groups. However, this study found no association between gonadotropin (LH, FSH), LH/FSH ratio and HOMA-IR (Tables 3, 4).

DISCUSSION

This study was designed to compare clinical characteristics, hormonal and metabolic parameters, including insulin resistance, between PCOS women who had normal BMI and PCOS women who presented as being overweight or obese. A study by Wongwananuruk et al. showed 30 percent of PCOS women had hypertension (4). This was higher than in our study which found that 13.9% had pre-hypertension. This could be the result of the lower age of PCOS patients in our study. The 22.3% prevalence of metabolic syndrome in this study was similar to the prevalence in a study by Pantasri et al. (6).

Table 3. Association between insulin resistance (HOMA-IR) with anthropometric and laboratory parameters in the overweight-obese group, BMI ≥ 23 kg/m^2 (Spearman correlation statistical analysis); p < 0.05

	(HOMA-IR)	
	r	*p*-value
Age	-0.222	0.193
Systolic blood pressure (mmHg)	0.157	0.362
Diastolic blood pressure (mmHg)	0.062	0.721
Height (cm)	0.196	0.251
Weight (kg)	0.675	< 0.001*
BMI (kg/m^2)	0.687	< 0.001*
Waist circumference (cm)	0.669	< 0.001*
Waist – height ratio	0.616	< 0.001*
Ferriman- Gallway Score	0.263	0.121
FAI	0.602	< 0.001*
Free testosterone (ng/dL)	0.459	0.005*
SHBG (nmol/L)	-0.604	< 0.001*
LH (mIU/mL)	-0.150	0.382
FSH (mIU/mL)	-0.061	0.723
LH/FSH ratio	-0.306	0.069
Cholesterol (mg/dL)	0.020	0.906
Triglycerides (mg/dL)	0.366	0.028*
HDL - C (mg/dL)	-0.508	0.002*
LDL – C (mg/dL)	0.157	0.361
TSH (μIU/mL)	0.057	0.743

BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FAI, free androgen index; FSH, follicular stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone

Table 4. Association between insulin resistance (HOMA-IR) and anthropometric and laboratory parameters in the normal weight group (BMI < 23 kg/m^2) (Spearman correlation statistical analysis); p < 0.05

	(HOMA-IR)	
	r	*p*-value
Age	-0.342	0.075
Systolic blood pressure (mmHg)	0.251	0.197
Diastolic blood pressure (mmHg)	0.217	0.268
Height (cm)	0.066	0.738
Weight (kg)	0.244	0.210
BMI (kg/m^2)	0.133	0.501
Waist circumference (cm)	0.299	0.122
Waist – height ratio	0.332	0.084
Ferriman- Gallway Score	-0.073	0.713
FAI	0.594	< 0.001*
Free testosterone (ng/dL)	0.543	0.003*
SHBG (nmol/L)	-0.654	< 0.001*
LH (mIU/mL)	0.257	0.186
FSH (mIU/mL)	0.093	0.637
LH/FSH ratio	0.222	0.257
Cholesterol (mg/dL)	-0.006	0.977
Triglycerides (mg/dL)	0.476	0.010*
HDL - C (mg/dL)	-0.140	0.477
LDL – C (mg/dL)	-0.063	0.752
TSH (μIU/mL)	0.015	0.940

BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FAI, free androgen index; FSH, follicular stimulating hormone; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone

In this study we used an HOMA-IR of 2.0 as the cut off value for insulin resistance based on a study by Siriraj Hospital, Thailand, that compared HOMA-IR with the 75 g oral glucose tolerance test as a standard test for the detection of impaired glucose tolerance in 250 PCOS Thai women. The Siriraj study proposed a cut off value of HOMA-IR of 2.0 which had sensitivity of 84.0%, specificity of 61.0%, positive predictive value of 35.0% and negative predictive value of 93.8% (5). There was a limitation with employing HOMA-IR >2 as an indicator of insulin resistance because the cut-off point of HOMA-IR is different for different races, ages and genders (21).

Comparison of clinical characteristics, biochemical and hormonal features between PCOS women with normal weight those with overweight or obesity, found fasting plasma glucose levels did not differ between groups, while fasting insulin was significantly higher in the overweight-obese group as was HOMA-IR (Table 2). This finding is compatible with a study by Ketel et al. which reported using an euglycemic hyperinsulinemic clamp to assess insulin sensitivity and found that normal weight PCOS women had insulin sensitivity equivalent to normal weight women without PCOS, while overweight PCOS women had remarkably higher insulin resistance than overweight women without PCOS (22). Similarly, in adolescent Thai PCOS women, Sawathipanich et al. reported that obese adolescents with PCOS had significantly higher HOMA-IR scores than those of obese adolescent girls without PCOS (23). However, the use of HOMA-IR in young normal weight patients with PCOS has limitations. Fulghesu et al. reported that the prevalence of hyperinsulinemia in young normal weight PCOS was not detected by HOMA and suggested using a 3-hour OGTT to detect early onset metabolic derangement in young normal weight PCOS individuals (24).

Regarding differences in sex hormone levels between overweight-obese PCOS and normal weight PCOS females, our study found a higher free androgen index and higher levels of free testosterone in the overweight group and higher SHBG and LH in the normal weight group. These findings corresponded with those of previous studies (24, 25). Measurement of gonadotropins found that the LH level in the overweight-obese group was lower than that of the normal weight group, which corresponds with a study by Katsikis et al. which showed that the LH level has a negative association with BMI (26). However, our study did not find differences in FSH or LH/FSH ratios between the groups. Differences in lipid profiles between overweight PCOS and normal weight PCOS women were similar to non PCOS populations, in that the overweight or obese population had higher triglycerides and lower HDL-cholesterol. Analysis of the association between insulin resistance index (HOMA-IR) and anthropometric factors in overweight-obese and normal weight PCOS found that in the overweight-obese group weight, BMI, waist circumference and waist-height ratio had a positive correlation with HOMA-IR, whereas in the normal BMI group those factors had no association with the insulin resistance index. These findings indicate that insulin resistance plays a major role in the pathophysiology of overweight-obese PCOS patients. These associations are explained by the relationship of both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) with metabolic disturbance in PCOS women. A study in Austria showed that in overweight-obese PCOS women, lower abdomen and upper back SAT had a significantly positive correlation with insulin resistance but that there was no relationship between SAT and insulin resistance in normal weight PCOS patients. The same study also reported a significantly positive correlation between triglycerides and SAT thickness at the neck, biceps, upper back, front, and lateral side of the chest wall (26). Fruzzetti et al. confirmed that BMI was a good predictor of metabolic abnormalities in PCOS based on the strong association between BMI and HOMA-IR, fasting insulin, blood pressure, and lipid profiles (27).

In our study, waist-height ratio was used as the anthropometric factor instead of waist-hip ratio based on the results of a study in China by Liu et al. which included 1,124 PCOS women that found waist-height ratio was a more accurate anthropometric indicator for predicting insulin resistance (by area under ROC curve and sensitivity of the test to predict insulin resistance state) compared to waist-hip ratio, waist circumference, and BMI. A waist-height ratio of 0.49 was used as the cut off value in that study (28).

Regarding the association between lipid profiles and insulin resistance, our study found that triglyceride levels had a positive association with HOMA–IR in both the normal weight and overweight-obese groups, while HDL cholesterol had a negative association with HOMA–IR only in the overweight-obese group. This finding indicates that low HDL cholesterol in overweight-obese subjects is of significance in predicting insulin resistance in that group.

The cut-off value of HOMA-IR as an indicator of insulin resistance can differ depending on the population being studied. A study in Thailand used an HOMA–IR of 2.0 (5) while a study from China used a cut off value of 2.77 (29).

In our study, PCOS women with features of metabolic syndrome had higher free testosterone and insulin levels compared with patients without features of metabolic syndrome, but the difference was not statistically significant due to the small sample size. The search for an association between insulin resistance index (HOMA-IR) and hormonal factors found in both the normal weight and overweight-obese groups that the free androgen index had a positive association with HOMA-IR and that SHBG had a negative association with HOMA-IR. However, this study did not find any association between gonadotropin (LH, FSH, LH/FSH ratio) and insulin resistance. Lee et al. studied clinical and biochemical features of PCOS women based on the quartile of HOMA-IR in 458 PCOS. That study showed significant differences in age, body weight, BMI, lipid profiles, glucose metabolic profiles, hs-CRP, apoprotein B, free testosterone, and SHBG between each of the quartiles of insulin resistance (30). Moran et al. studied the relationship between insulin resistance (expressed as glucose/insulin ratio) and gonadotropin dissociation (increased LH level with normal FSH level) in obese and non-obese women with PCOS. They found that insulin resistance did not appear to be related to gonadotropin dissociation (31).

CONCLUSIONS

PCOS is a disease with a high diversity in pathogenesis, clinical manifestations, and complications. Abnormal ovarian steroidogenesis and abnormal folliculogenesis can lead to anovulation, hyperandrogenemia, and infertility. Due to the diversity in the pathogenesis of PCOS, clinical management guidelines should be individualized and may differ between normal weight PCOS and overweight-obese PCOS patients. This study showed differences in the association of factors with insulin resistance between normal weight PCOS and overweight-obese PCOS. Interestingly, triglycerides, the free androgen index and SHBG played a significant role in identifying the level of insulin resistance in both groups of PCOS. Further studies comparing normal weight and overweight-obese PCOS may lead to better understanding of insulin resistance in PCOS.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Authors contribution

K.C.: conceptualization, methodology, implementation, data analysis, writing, review and editing; I.W.: methodology, subject recruitment; A.P.: investigations; P.C.: conceptualization, supervision.

Data availability statement

The data used in this study are not publicly available due to participant privacy but are available from the corresponding author upon reasonable request.

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Does Chin-Throat Length Relate to Oropharyngeal Volume, Minimum Axial Area, and Polysomnographic Indices?

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ABSTRACT

OBJECTIVE To evaluate the correlation between chin-throat length and oropharyngeal volume, minimum axial area, and polysomnographic indices in patients undergoing orthodontic treatment.

METHODS The study enrolled 73 patients (35 men and 38 women) who met the inclusion criteria. The face scanner created a 3D facial simulation, and chin-throat length was subsequently measured. 3D CBCT images were used to simulate 2D lateral cephalometric images. Oropharyngeal volume and minimum axial area were determined using Dolphin imaging software, and airway function was assessed through unattended at-home overnight polysomnography. Pearson correlation coefficients were then used to determine the correlations between chin-throat length and oropharyngeal volume, minimum axial area, and polysomnographic indices. Additional correlations were explored between age, BMI, cephalometric variables, and oropharyngeal volume, and minimum axial area. Finally, multiple regression analysis was used to analyse the factors having an influence on the correlations.

RESULTS Chin-throat length was positively correlated with oropharyngeal volume and minimum axial area. SNB, ANB, Co-Gn, and Go-Gn were also observed to be positively correlated with oropharyngeal volume and minimum axial area. Multiple regression analysis demonstrated that the factor influencing the correlation of chin-throat length with oropharyngeal volume and with minimum axial area was mandibular length; however, the correlations were only observed among men. No correlation was evident between chin-throat length and polysomnographic indices.

CONCLUSIONS Chin-throat length is positively correlated with oropharyngeal volume and minimum axial area but has no association with polysomnographic indices. Mandibular length may influence upper airway dimensions.

KEYWORDS chin-throat length, oropharyngeal volume, minimum axial area, polysomnographic indices

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic sleep-related disorder that has been widely studied in orthodontics over the past decade because of the severity and prevalence of the disease, which affects approximately 9% to 38% of the adult population worldwide (1). OSA is a multifactorial disorder, and its associated risk factors include obesity, age (i.e., increasing risk with age), male gender, metabolic syndrome, craniofacial anatomy, and upper airway abnormalities (2). Obesity is one of the major risk factors of OSA, but only a small number of patients with OSA in Asia are obese (3). Given the apparently lesser role of obesity in OSA among Asians, craniofacial anatomical factors might play a key role in the pathogenesis of OSA in Asian populations (4). Several researchers have investigated using craniofacial anatomy as a predictive factor for OSA because using polysomnography (PSG), the standard approach, features has several disadvantages, namely high cost, limited accessibility, and a need for technician control (5). Studies on craniofacial anatomy as a predictive factor have focused on skeletal features and soft tissues. In this context, Hong et al. investigated the impact of mandibular position on pharyngeal airway volume using 3D analysis (6). Their findings highlighted a noteworthy correlation which indicates that anterior mandibular position is associated with increased upper pharyngeal airway volume. However, the use of skeletal features in evaluations necessitates radiographic imaging modalities, potentially diminishing clinical utility. By contrast, the use of soft tissue features does not require the use of those modalities and may represent a clinically useful approach to OSA prediction. Various soft tissue studies have investigated the relationship between soft tissue phenotypes and OSA. Mallampati score, tonsil size, and neck circumference have been identified as potential risk factors for factors potentially related to OSA incidence, but other soft tissue features, including chin-throat length have been neglected (7, 8).

In orthodontics, chin-throat length is one of the main parameters used to evaluate potential orthodontic or orthognathic interventions, as well as to predict aesthetic outcomes (9). Some studies have determined that mandibular setback surgery is contraindicated in patients with a short chin-throat length because this procedure might negatively affect their upper airway (10). However, no solid evidence has demonstrated that the relationship between chin-throat length and upper airway morphology can be used to infer the risk of OSA.

Due to the clinical usefulness of soft tissue in predicting OSA and the lack of evidence supporting the association between chin-throat length and upper airway morphology, this study aimed to evaluate the correlations between chin-throat length and oropharyngeal volume, minimum axial area, and polysomnographic indices in patients undergoing orthodontic treatment using a three-dimensional (3D) face scanner, cone-beam computed tomography (CBCT), unattended at-home overnight PSG (SOMNOlab 2), and Dolphin imaging software.

METHODS

Subjects and selection criteria

This study was approved by the human experimentation committee of our institution (No. 68/2563). The study sample comprised 73 Thai patients (35 men and 38 women) who underwent orthodontic treatment and orthodontic consultation from October 2020 to December 2021. All patients who met the inclusion criteria were invited to participate in the study.

The inclusion criteria were age between 15 and 35 years, being in good health, and having a BMI of less than 23 kg/m^2. Patients with craniofacial syndromes or systemic diseases and those who had received previous orthodontic treatment or orthognathic surgery were excluded from the study. All patients signed the consent forms, and for those who were under the age of 18, the consent forms were signed by their parents or legal guardians.

Study variables

The independent variables and outcome variables of the study are specified in Table 1.

Face scanning and measurement

Patients' faces were scanned using an Accu 3D face scanner (Digident Image Technology, Taichung, Taiwan) after which facial simulations were generated. Soft tissue landmarks, namely the soft tissue menton (Me') and neck-throat

Table 1. Independent variables and outcome variables

Independent variables	Outcome variables
Chin-throat length (mm)	Upper airway dimensions
Age (year)	- Oropharyngeal volume (mm^3)
BMI (km/m^2)	- Minimum axial area (mm^2)
Cephalometric variables	Polysomnographic indices
- SNA (degree)	- AHI (events/hour)
- SNB (degree)	- ODI (events/hour)
- ANB (degree)	- Lowest oxygen saturation (%)
- FMA (degree)	- Average oxygen saturation (%)
- Co-A (mm)	
- Co-Gn (mm)	
- Go-Gn (mm)	

point (C-point), were identified (Fig. 1A). In accordance with the approach of Naini and Gill, (11) chin-throat length was defined as the distance from the Me' to C-point (Fig. 1B).

Upper airway measurement

CBCT scans were taken using MobiiScan (NSTDA, Bangkok, Thailand) with the following parameters: 90 kV, 8 mA, 22 cm x 18 cm field of view, and 0.4 mm voxel size. DICOM data obtained from CBCT were processed using third-party software (Dolphin Imaging Software Version 11.9, Dolphin Imaging & Management Solutions, Chatsworth, CA, USA). During the scanning process, conscious participants were instructed to consistently maintain maximum intercuspation, position the tongue against the hard palate, breathe in a normal manner, and refrain from swallowing.

The plane orientation was manually applied for each patient using the approach adopted by Guijarro-Martinez and Swennen (12). All CBCT images were examined using a craniocervical inclination that was defined by the intersection between the S-N plane and the C2p-C2lp plane (from the uppermost posterior point of the second cervical vertebra to the lowermost posterior point of the second cervical vertebra). This angle must fall within a range of 90° to 110°, otherwise the upper airway dimension may be inaccurately calculated (13). Subsequently, the threshold value (average: 70) of the upper airway morphology was manually adjusted until the pharyngeal airway was adequately depicted. The upper airway morphology was measured using Guijarro-Martinez and Swennen's (12) method, which is based on oropharyngeal volume (Fig. 2A) and minimum axial area (Fig. 2B). The Dolphin imaging software automatically calculated the oropharyngeal airway volume (mm^3) and minimum axial area (mm^2).

Airway function assessment

The patients underwent evaluation of their upper airway function. The evaluation was conducted using an unattended at-home overnight PSG system, SOMNOlab 2 (Fig. 3). Expert specialists gave the patients comprehensive instructions on the precise assembly and operation of the SOMNOlab 2 monitor. The PSG recordings were analysed by a board-qualified physician. OSA was diagnosed in patients whose apnea-hypopnea index (AHI) was more than five events per hour.

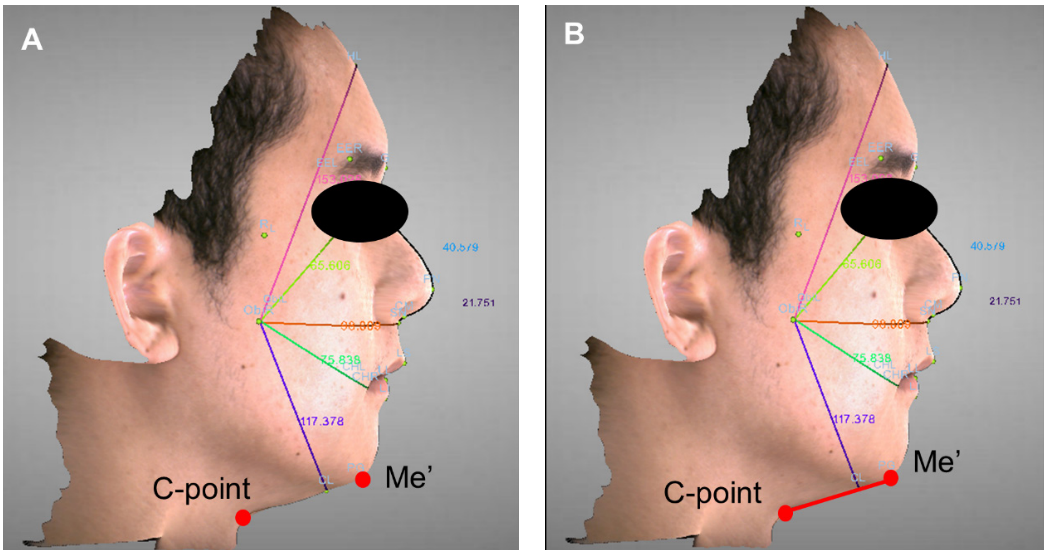

Figure 1. Landmarks and measurements. (A) Soft tissue landmarks: soft tissue menton (Me') and neck-throat point (C-point). (B) Chin-throat length measurement.

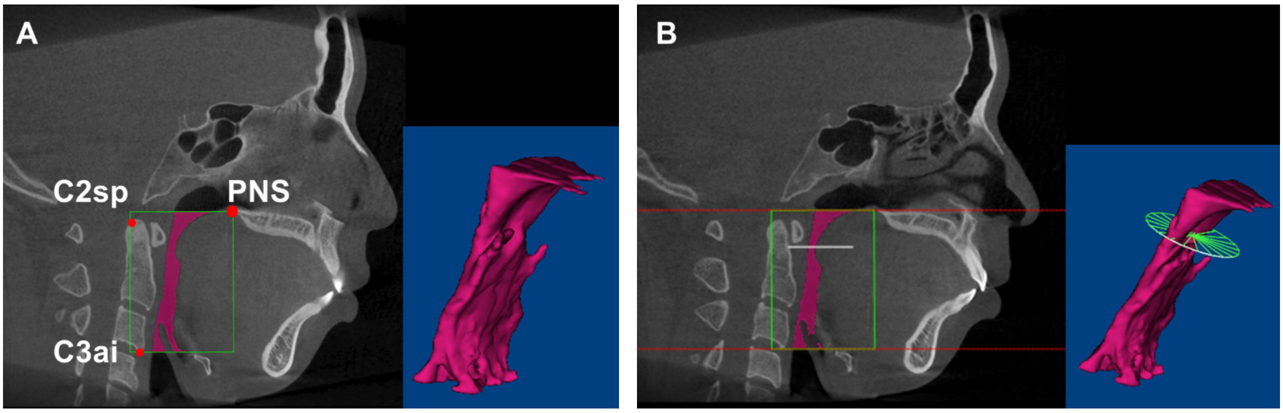

Figure 2. Landmarks and measurements of upper airway dimensions. (A) Oropharyngeal volume landmarks: posterior nasal spine (PNS), most super posterior point of the second cervical vertebrae (C2sp), and most anteroinferior aspect of the third cervical vertebrae (C3ai). (B) Minimum axial area.

Figure 3. An unattended at-home overnight PSG system (SOMNOlab 2)

Cephalometric analysis

Two-dimensional (2D) lateral cephalometric images were simulated on the basis of 3D CBCT images. Linear and angular measurements of the angle indicating the horizontal position of the maxilla relative to the cranial base (SNA), the angle indicating the horizontal position of the mandible relative to the cranial base (SNB), the angle measuring the relative position of the maxilla to the mandible (ANB), the angle between the Frankfort horizontal plane and the mandibular plane (FMA), the maxillary length from the condylion to A point (Co-A), the mandibular length from the condylion to gnathion (Co-Gn), and the mandibular length from the gonion to gnathion (Go-Gn) were recorded.

Statistical analysis

The sample size was calculated using G*Power (Version 3.1.9.4, University of Kiel, Kiel, Germany). For a correlation of 0.4, a power of 80%, and a significance level of 5%, the final minimum sample size was 47 patients.

To test the reliability of the measurements, the chin-throat length and upper airway morphology of randomly selected patients were measured. Over the subsequent 4 weeks, the measurements of the patients were retaken by the same examiner. Intraclass correlation coefficients (ICCs) was then used to perform the intra-variation assessment.

SPSS Version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to calculate all statistical results, and descriptive analysis was applied to determine the means and standard deviations of the data. The normality of the variables was assessed using the Kolmogorov-Smirnov test. The results indicated that the distribution of all variables did not significantly deviate from a normal distribution ($p > 0.05$), supporting the assumption of normality for subsequent statistical analyses. The correlations between chin-throat length and upper airway dimensions and function were tested using the Pearson correlation coefficient. The results were considered statistically significant at $p < 0.05$. The Potentially influencing factors were assessed through multiple regression analysis using a stepwise method.

RESULTS

Data were collected from 73 patients (35 men and 38 women) ranging in age from 15 to 35 years (mean age: 22.70 ± 5.15 years). Patient BMI ranged from 15.78 to 23.00 kg/m^2 (mean BMI: 20.58 ± 1.92 kg/m^2), and the mean chin-throat length was 40.76 ± 5.72 mm.

CBCT imaging was used to categorise patients into skeletal class I (23 patients), class II (28 patients), and class III (22 patients). The means and standard deviations of chin-throat length divided by sagittal skeletal pattern were calculated, and the lengths of the groups were as follows: 41.58 ± 5.07 mm in skeletal class I patients, 38.94 ± 6.29 mm in class II patients, and 43.72 ± 4.81 mm in class III patients. The CCA of all patients fell within the range of 90° to 110° (mean CCA: 96.71 ± 6.57 degrees). The descriptive analysis of all variables with respect to gender and OSA diagnosis is presented in Table 2.

The airway function of 73 patients was measured. Four polysomnographic indices were recorded: AHI, oxygen desaturation index (ODI), lowest oxygen saturation, and average oxygen saturation. Eight patients, comprising 5 men and 3 women, with ages ranging from 15 to 31 years (mean age: 23.25 ± 5.25 years), were diagnosed with OSA based on an AHI exceeding five events per hour (range: 6.0 to 30.3 events per hour). The means and standard deviations of the polysomnographic indices are detailed in Table 2.

Pearson correlation coefficients were then used to determine the relationship of oropharyngeal volume and minimum axial area with chin-throat length and other factors, including age, BMI, and cephalometric variables. Oropharyngeal volume and minimal axial area were slightly positively correlated with chin-throat length. SNB, ANB, Co-Gn, and Go-Gn were each correlated with both oropharyngeal volume and minimum axial area. Additionally, chin-throat length was

Table 2. Means and standard deviations of all variables with respect to gender and OSA diagnosis

	Gender			OSA		
Variables	**Male (n = 35) Mean ± SD**	**Female (n = 38) Mean ± SD**	***p*-value**	**Non-OSA (n = 65) Mean ± SD**	**OSA (n = 8) Mean ± SD**	***p*-value**
BMI (kg/m^2)	21.21±1.94	20.00±1.73	0.007**	20.54±1.96	20.86±1.66	0.630
Chin-throat length (mm)	40.99±5.41	40.54±6.06	0.730	40.76±5.54	40.74±7.49	0.990
Cephalometric variables						
- SNA (degree)	83.30±4.05	84.49±3.51	0.190	83.88±3.74	83.80±4.30	0.950
- SNB (degree)	80.26±6.47	82.74±5.42	0.090	81.28±5.86	83.36±7.15	0.450
- ANB (degree)	3.02±4.92	1.74±4.99	0.280	2.59±4.83	0.43±5.40	0.310
- FMA (degree)	23.59±6.88	24.88±5.36	0.380	24.23±6.09	25.46±6.86	0.640
- Co-A (mm)	96.00±5.13	89.36±5.05	< 0.001***	92.56±6.16	92.70±5.35	0.940
- Co-Gn (mm)	131.31±8.59	124.13±8.53	0.001**	127.06±9.39	131.65±6.53	0.100
- Go-Gn (mm)	82.63±7.21	78.13±5.92	0.006**	80.13±7.17	81.80±6.36	0.500
Upper airway dimensions						
- Oropharyngeal volume (mm^3)	14,508.88±5,239.69	12,590.92±4,842.60	0.110	13,365.75±5,189.86	14,399.50±4,392.79	0.550
- Minimum axial area (mm^2)	146.05±78.32	135.02±74.91	0.550	142.27±76.10	125.75±80.80	0.590
Polysomnographic indices						
- AHI (events/hour)	2.70±5.44	1.45±3.29	0.240	0.80±0.93	12.21±8.04	0.005**
- ODI (events/hour)	1.78±2.23	1.31±1.77	0.320	1.36±1.82	2.97±2.90	0.160
- Lowest oxygen saturation (%)	85.82±5.05	85.44±6.51	0.780	86.93±5.42	82.37±8.12	0.250
- Average oxygen saturation (%)	96.63±1.36	97.39±0.71	0.005*	97.03±1.17	96.98±0.73	0.870

SD, standard deviation; statistically significant difference, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

correlated with oropharyngeal volume and minimal axial area in male patients only (Table 3).

The correlations between chin-throat length and polysomnographic indices were further analysed using the Pearson correlation coefficient. No correlation was noted between chin-throat length and upper airway function as represented in Table 4.

The Pearson correlation coefficient was also used to assess the relationship between oropharyngeal volume and minimum axial area and polysomnographic indices. No significant correlations were observed between oropharyngeal volume and polysomnographic indices. Similarly, no significant correlations were detected between minimum axial area and polysomnographic indices, as outlined in Table 5.

The influencing factors of oropharyngeal volume and minimum axial area were then investigated using multiple regression analysis with a stepwise method, and age, gender, BMI, cephalometric variables (SNA, SNB, ANB, FMA, CO-A, Co-Gn, and Go-Gn), and chin-throat length were included as independent variables. Multiple regression analysis indicated that Co-Gn was related to oropharyngeal volume (R^2 = 17.8%, $p < 0.01$) and minimum axial area (R^2 = 14.7%, $p = 0.01$; Table 6).

The intraexaminer reliability tests for chin-throat length and oropharyngeal volume revealed

Table 3. Pearson correlation coefficients for chin-throat length, age, BMI, and cephalometric variables in relation to oropharyngeal volume and minimum axial area.

		OP (mm^3)	*p*-value	Min (mm^2)	*p*-value
TL (n = 73)	*r*	0.26*	0.029*	0.193	0.110
	R^2	0.068		0.037	
TL male (n = 35)	*r*	0.449**	< 0.010**	0.43*	0.011*
	R^2	0.202		0.185	
TL female (n = 38)	*r*	0.094	0.580	−0.017	0.920
	R^2	0.009		0.000	
Age (year)	*r*	−0.074	0.542	−0.137	0.259
	R^2	0.005		0.019	
BMI (km/m^2)	*r*	−0.076	0.528	−0.115	0.344
	R^2	0.006		0.013	
SNA (degree)	*r*	0.079	0.518	0.166	0.170
	R^2	0.006		0.028	
SNB (degree)	*r*	0.337*	0.004*	0.34*	0.004*
	R^2	0.114		0.116	
ANB (degree)	*r*	−0.351**	< 0.010**	−0.289*	0.015*
	R^2	0.123		0.084	
FMA (degree)	*r*	−0.108	0.372	−0.172	0.154
	R^2	0.012		0.030	
Co-A (mm)	*r*	0.187	0.121	0.200	0.096
	R^2	0.035		0.04	
Co-Gn (mm)	*r*	0.422**	< 0.010**	0.384**	< 0.010**
	R^2	0.178		0.147	
Go-Gn (mm)	*r*	0.404**	< 0.010**	0.341**	< 0.010**
	R^2	0.163		0.116	

TL, chin-throat length; OP, oropharyngeal volume; min, minimum axial area; R^2, coefficient of determination; statistically significant difference, *$p < 0.05$; **$p < 0.01$.

Table 4. Pearson correlation coefficients for chin-throat length in relation to polysomnographic indices.

		AHI	*p*-value	ODI	*p*-value	Lowest oxygen saturation	*p*-value	Average oxygen saturation	*p*-value
TL (n = 73)	*r*	-0.028	0.818	-0.074	0.533	0.141	0.246	0.062	0.608
	R^2	0.001		0.284		0.020		0.004	

TL, chin-throat length; R^2, coefficient of determination.

Table 5. Pearson correlation coefficients for oropharyngeal volume and minimum axial area in relation to polysomnographic indices.

		AHI	*p*-value	ODI	*p*-value	Lowest oxygen saturation	*p*-value	Average oxygen saturation	*p*-value
OP (mm³)	*r*	0.118	0.318	−0.086	0.471	0.010	0.933	0.180	0.128
	R^2	0.014		0.007		0.000		0.032	
Min (mm²)	*r*	0.040	0.743	−0.102	0.399	−0.019	0.878	0.196	0.104
	R^2	0.002		0.010		0.000		0.038	

OP, oropharyngeal volume; Min, minimum axial area; R^2, coefficient of determination.

Table 6. Multiple regression analysis conducted on oropharyngeal volume and minimum axial area (independent variables: age, BMI, cephalometric variables, and chin-throat length).

Variables		Coefficient	*p*-value	β	R^2
Dependent	Independent				
Oropharyngeal volume	Mandibular length (Co-Gn)	240.314	< 0.010	0.42	0.178
	Constant	−17,015.672	0.037		
Minimum axial area	Mandibular length (Co-Gn)	3.180	0.010	0.38	0.147
	Constant	−265.346	0.029		

β, standardised coefficient β; coefficient, unstandardised coefficients; R^2, coefficient of determination.

strong intraclass correlations (r = 0.991 and r = 0.999, respectively), indicating high measurement reliability.

DISCUSSION

The current study identified a slight correlation between chin-throat length and oropharyngeal volume and minimal axial area. Additionally, correlations were observed between cephalometric variables (SNB, ANB, Co-Gn, Go-Gn) and oropharyngeal volume, as well as minimal axial area. However, no correlation was observed between chin-throat length and polysomnographic indices. Co-Gn was identified as an influencing factor in the relationship between chin-throat length and oropharyngeal volume and minimum axial area.

Two-dimensional lateral cephalometry has been used to assess the dimensions of the upper airway. However, because applying 2D evaluation to 3D structures is impractical and because 2D lateral cephalometry cannot be used for volumetric measurement, this technique is not particularly effective for evaluating airway dimensions (14). Several imaging techniques can be used for upper airway assessment, namely CBCT, multidetector CT (MDCT), magnetic resonance imaging (MRI), endoscopy, and optical coherence tomography (12). CBCT has certain advantages over other imaging techniques, e.g., the radiation dose from CBCT is lower than that of MDCT. Additionally, accessibility is greater and costs of CBCT are lower than those of MRI (12). The accuracy and reliability of CBCT for upper airway assessment has been demonstrated and thus, CBCT is widely used to evaluate the upper airway (12).

The use of position-dependent upper airway dimensions has also been explored. Tsuiki et al. (15) indicated that a change in position from upright to supine influenced the dimensions of the velopharynx and oropharynx areas. Therefore, it is crucial to consider this factor. Consequently, patients in this study were scanned in a supine position using MobiiScan.

Direct clinical evaluation of facial soft tissue landmarks has also been used to predict OSA, an approach which avoids the need for radiographic examination. Early detection of OSA may be aided by clinical detection of pharyngeal airway constriction. Studies have identified a relationship between surface facial dimensions and upper airway structures in patients with OSA, implying that facial soft tissue measurement may be a valuable tool in phenotyping patients with OSA (16). However, the correlations of chin-throat length with upper airway dimensions at the oropharyngeal level and with polysomnographic indices have not been investigated previously.

The distance between the neck-throat point and soft-tissue menton is known as the chin-throat length (17). Chin-throat length is a commonly used criterion in the diagnosis and treatment planning of patients with mandibular and chin deformities who require anteroposterior correction (18). For mandibular length, a measure of 38 to 48 mm is considered normal, with Class III cases being longer and Class II cases being shorter (17). Chin-throat length differs significantly between the three skeletal sagittal types, with the chin-throat length of skeletal class II patients being substantially shorter than those of skeletal class I and III patients (9). The means and standard deviations of chin-throat length categorised by sagittal skeletal patterns were also reported in this study: 41.58 ± 5.07 mm in class I, 38.94 ± 6.29 mm in class II, and 43.72 ± 4.81 mm in class III. Related to the potential gender-related variations in chin-throat length, a 3D cephalometric investigation conducted by Wang et al. (19). disclosed significant distinctions in jaw length between males and females. Conversely, that study observed no statistically significant differences in soft tissue chin-throat length between genders. These findings reported by Wang et al. are consistent with the outcomes of the present study, where significant differences in jaw length (maxillary and mandibular length) between genders were identified; however, no statistically significant gender-based difference was discerned in chin-throat length.

The upper airway can be divided into three parts: the nasopharynx, oropharynx, and hypopharynx. In this study, our primary focus was on oropharyngeal volume because the oropharynx is the part most likely to be influenced by jaw position and the surrounding soft tissue. Changes in the spatial arrangement and dimensions of oral and pharyngeal soft tissues can occur due to shifts in the positions of the soft palate, tongue, and associated muscles (20). Individuals with Angle Class II malocclusion tend to exhibit a narrower oropharynx than those with Angle Class I or III malocclusion (21). Additionally, for predicting OSA, the association of minimum axial area with craniofacial structures has been investigated. A study reported variations in minimum axial area depending on skeletal pattern (22). With consideration for these findings, the primary objective of this study was to explore the relationship between chin-throat length and pharyngeal airway dimensions. Consequently, we selected oropharyngeal volume and minimum axial area as the key parameters for analysis.

Slight positive correlations between chin-throat length and oropharyngeal airway and minimum axial area were identified in this study. The constriction of the anatomical features of the airway does not always result in reduced respiratory performance, leading in turn to OSA, but some studies have demonstrated a correlation between oropharyngeal volume, minimum cross-sectional area, and AHI (23). Thus, the chin-throat length measurement may be able to serve as a parameter for evaluating oropharyngeal volume and minimum axial area, thereby promoting the early detection of OSA.

The current study did not identify any significant differences in oropharyngeal volume and minimum axial area between genders. This differs from research findings that have indicated a larger and longer upper airway in males compared to females (24). Nonetheless, no study has investigated the associations between chin-throat length and oropharyngeal volume and minimum axial area in men and women. When gender was considered in this study, correlations between chin-throat length and oropharyngeal volume and minimum axial area were only observed in men. Consequently, gender appears to be an influencing factor in the relationship between chin-throat length and upper airway parameters, specifically at the oropharyngeal level.

Multiple regression analysis was used to evaluate the influencing factors between chin-throat length and oropharyngeal volume and minimum axial area. The results, presented in Table 3, indicate an association between Co-Gn and oropharyngeal volume as well as minimum axial area. It is widely recognised that obesity, age (older), male gender, and craniofacial morphology influence OSA (2). Chin-throat length exhibited a positive correlation with oropharyngeal volume and minimum axial area, but other factors, particularly Co-Gn, were also found to be related to oropharyngeal volume and minimum axial area. Therefore, oropharyngeal volume and minimum axial area are influenced by a combination of factors, and Co-Gn might actually be the most significant factor affecting them.

In this study, chin-throat length was not correlated with the polysomnographic indices of AHI, lowest oxygen saturation, or average oxygen saturation. Eight patients (11.42%) were diagnosed as having OSA. Further, no correlation was observed between oropharyngeal volume, minimum axial area, and polysomnographic indices. Other studies focused on individuals with OSA have suggested that the volume of the velopharyngeal level can serve as a valuable indicator of the severity of AHI and lowest oxygen saturation (25), contrasting with the current study. However, only healthy participants between the ages of 15 and 35 with a normal BMI were included in this study. While craniofacial features may play an essential role in the pathophysiology of OSA in Asian populations (4), the syndrome was found to be occur in approximately 7% of Asian populations (26). Therefore, we suggest collecting larger samples of Asian patients with OSA to further investigate whether polysomnographic indices are related to chin-throat length, oropharyngeal volume, and minimum axial area.

In this study, chin-throat length was correlated with oropharyngeal volume and minimum axial area. Some operations, such as mandibular setback surgery, might negatively affect the upper airway (10); to reduce the risk of negative outcomes, measuring chin-throat length could serve as a valuable screening approach for upper airway assessment when planning orthodontic or orthognathic surgical treatment.

This study makes certain contributions to the literature, but a key limitation should be mentioned. CBCT was performed while the patients were awake. This is problematic because, as various studies using 2D lateral cephalometry and CBCT have demonstrated, the position of patients affects their airway dimensions (27). A static supine position does not accurately depict the moving and changing positions that occur during sleep (28), and whether the patient is asleep or awake has a crucial influence on airway dimensions (28). Therefore, CBCT imaging performed with patients in the supine position is not ideal because it does not allow for accurate simulation of sleeping conditions.

CONCLUSIONS

A slight positive correlation was identified between chin-throat length and oropharyngeal volume and minimum axial area. However, this correlation was only observed among men. Additionally, SNB, ANB, Co-Gn, and Go-Gn demonstrated correlations with both oropharyngeal volume and minimum axial area. The crucial variables influencing the relationship between chin-throat length and oropharyngeal volume and minimum axial area may include mandibular length. The present study found no correlation between chin-throat length and polysomnographic indices.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contribution

Conceptualization, W.T., N.S., W.P., D.J., T.S., T.S., K.T.; Methodology, W.T., N.S., D.J., T.S., K.K., K.T.; Software, N.S., K.T.; Validation, W.T., N.S., W.P., T.S., K.T.; Formal analysis, W.T., T.S.; Investigation, W.T., N.S., K.K., K.T.; Resources, N.S., D.J., K.T., Data curation, T.S.; Writing—original draft preparation, W.T.; Writing—review and editing, N.S., D.J., K.K., P.K., W.T., visualization, K.T.; Supervision, K.T.; Project administration, K.T.All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

This study was approved by the Human Experimentation Committee of Chiang Mai University's Faculty of Dentistry (No. 68/2563).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

All data are available upon request.

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Breaches in Infection Prevention and Controls Discovered During an Outbreak Investigation of Two Unlinked Cases of *Pseudomonas aeruginosa* Bloodstream Infections in a Cardiovascular Thoracic Surgery Unit

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ABSTRACT

Two patients with *Pseudomonas aeruginosa* bloodstream infections were diagnosed a week apart in a cardiovascular thoracic (CVT) surgery unit where there had been no cases of *P. aeruginosa* infections in the preceding 6 months. An outbreak investigation was conducted. Medical records were reviewed to identify potential common exposure in both patients. Outbreak investigation procedures included cultures of intravenous infusions and various solutions in the operating theatre and the general CVT surgery unit, the intensive care unit and the intermediate care unit, and monitoring compliance with the central line associated bloodstream infection prevention bundle. Both the blood cultures of the two patients as well as the liquid soap used for hand washing in the unit grew *P. aeruginosa*. However, there were three clonalities of isolates, the first from patient A, the second from patient B, and the third from the liquid soap. Other intravenous infusions and various solutions, i.e., normal saline solution, lactate ringer solutions, solutions for cardiopulmonary bypass circuits, and skin antisepsis, did not grow potential pathogens. In conclusion, although these were unlinked cases, investigation of the cases uncovered breaches in infection control practices and provided an opportunity to improve the infection control strategies in our institution..

KEYWORDS *P. aeruginosa*, bloodstream infection, outbreak, outbreak investigation, infection control

INTRODUCTION

Pseudomonas aeruginosa is an aerobic gram-negative bacterium that is ubiquitous in the environment, including in soil, water and plants (1). It is one of the pathogens most frequently implicated in healthcare-associated infections (1). Outbreaks of *P. aeruginosa* related to the hospital environment have been reported (2-7). Here we present two cases of *P. aeruginosa* bloodstream infections (BSIs) which occurred in July 2020, a week apart, in the general cardiovascular thoracic (CVT) surgery unit. As there had been no cases of *P. aeruginosa* BSI in the previous 6 months in this unit, we suspected a common source of the outbreak, prompting an investigation to identify possible reservoirs and modes of transmission as well as to implement infection control measures to prevent future outbreaks.

METHODS

Maharaj Nakorn Chiang Mai Hospital is a 1,400-bed, tertiary-care, university-affiliated hospital. The Division of Cardiovascular Thoracic (CVT) surgery performs approximately 700-800 cardiac surgeries a year. The detection of *P. aeruginosa* in blood cultures of two patients within a week triggered an investigation by the infection control team. Both patients had clinical signs and symptoms of bloodstream infection. We reviewed the medical records and identified potential sources of exposure common to both patients.

Outbreak investigation procedures

1. Compliance with CLABSI prevention bundle

As the patients had bloodstream infections and it was unproven if they were central venous catheter (CVC) related, we focused on infection control measures for CVC insertion and dressings. To that end, we randomly observed the practice of central line insertion after this occurrence.

2. Cultures of intravenous infusions and various solutions

Intravenous infusions, including NSS, lactate ringer solution (LRS), solutions used in operating procedures, and solutions used with surgical wound dressings in the affected units, i.e., liquid soap for hand washing and antiseptic solutions for wound dressings, were randomly sampling for cultures.

Microbiology

Culture and drug susceptibility testing were performed at the Microbiology Unit, Diagnostic Laboratory, Maharaj Nakorn Chiang Mai Hospital. Colonies were identified by MALDI-TOF (VITEK MS, Biomerioux, Marcy l'Etoile, France). Antimicrobial susceptibility testing was performed using broth microdilution techniques (THAN2F, Sensititre, ThermoFisher, Massachusetts, USA). In addition to the two isolates from hemocultures, all specimens that grew *P. aeruginosa* from environmental samples were sent for genotypic study using the multilocus sequence typing (MLST) method at the microbiology laboratory, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital.

Ethical approval

This study was exempt from review by Research Ethics Committee of Faculty of Medicine, Chiang Mai University (certificate of exemption MED 7555/2020). Informed consent regarding the case details for publication in medical journals was obtained from the parent of patient A (as patient A had died) and from patient B.

RESULTS

Description of the cases

Patient A was a 20-year-old male admitted to the general CVT surgery unit due to a sternal wound infection from *S. aureus* on April 27th, 2020 following a Bentall procedure in January 2020. He underwent surgery in operating room (OR) "A" by surgeon team "A" on June 30th, 2020 where the Bentall operation was re-performed. Two central venous catheters were inserted, the first of which was inserted in the intermediate care unit (IMCU) and the second in the OR. He was subsequently transferred from the intensive care unit (ICU) to IMCU on July 8th, 2020 and then to the general CVT surgery unit, bed number 14, on July 9th, 2020. The tip of the first central venous catheter, collected on July 10th, 2020, grew *P. aeruginosa*. His blood cultures were collected on July 11th, 2020 also grew *P. aeruginosa*.

Patient B was a 61-year-old female admitted to the general CVT surgery unit on July 3rd, 2020 for tricuspid valve annuloplasty. She underwent surgery in OR "B" by surgeon team "B" on July 9th, 2020 and was transferred from the ICU to IMCU on July 10th, 2020 then to the general CVT surgery unit, bed number 15, on July 11th, 2020. Her blood cultures were collected on July 18th, 2020 grew *P. aeruginosa*. Echocardiography performed on July 23th, 2020 revealed vegetation at the anterolateral tricuspid valve annulus which was identified as prosthetic valve endocarditis.

All wound dressings for both patients were applied by the same surgical team. There were no other patients diagnosed with *P. aeruginosa* pneumonia or UTI in the general CVT surgery unit in the preceding 6 months. Both patients recovered from BSI following catheter removal and a course of antibiotics and were discharged from the hospital. The timelines for both patients are shown in Figure 1 and the room maps of the general CVT surgery unit and IMCU are shown in Figure 2.

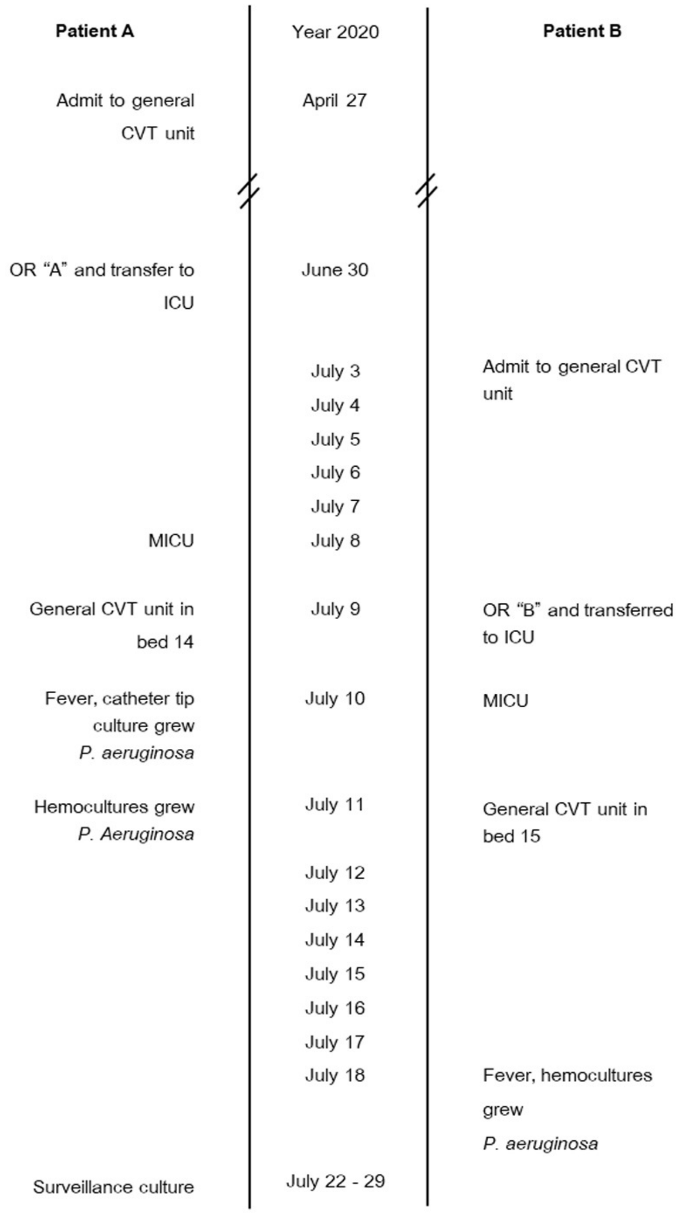

Figure 1. Timeline of the two patients with *P. aeruginosa* bloodstream infections

Antibiotic susceptibility patterns of clinical isolates

Antibiotic susceptibility (DST) patterns of *P. aeruginosa* isolates from patients A and B are shown in Table 1. Two peripheral blood cultures from patient A had the same DST pattern, whereas cultures of from the catheter tip had a different DST pattern for imipenem. In the case of patient B, DST was the same for the peripheral blood cultures. No catheter tips were sent for culture.

Multilocus Sequence Typing (MLST) profile for *P. aeruginosa*

There were 3 clonalities of isolates: ST918 was discovered in the isolates from patient A, ST3393 from patient B, and ST381 from liquid soap in the general CVT surgical unit. The results are shown in Table 2.

Compliance with central line-associated bloodstream infection (CLABSI) bundles

Fifteen central venous catheter insertions were investigated after this outbreak. All but one followed the CLABSI bundles, including having only well-trained healthcare personnel performing the procedure, following appropriate hand hygiene practices, using 2% alcoholic chlorhexidine for skin antisepsis, use of maximum sterile barriers, selecting optimal sites (avoiding the femoral vein), and the wearing of appropriate personal protective

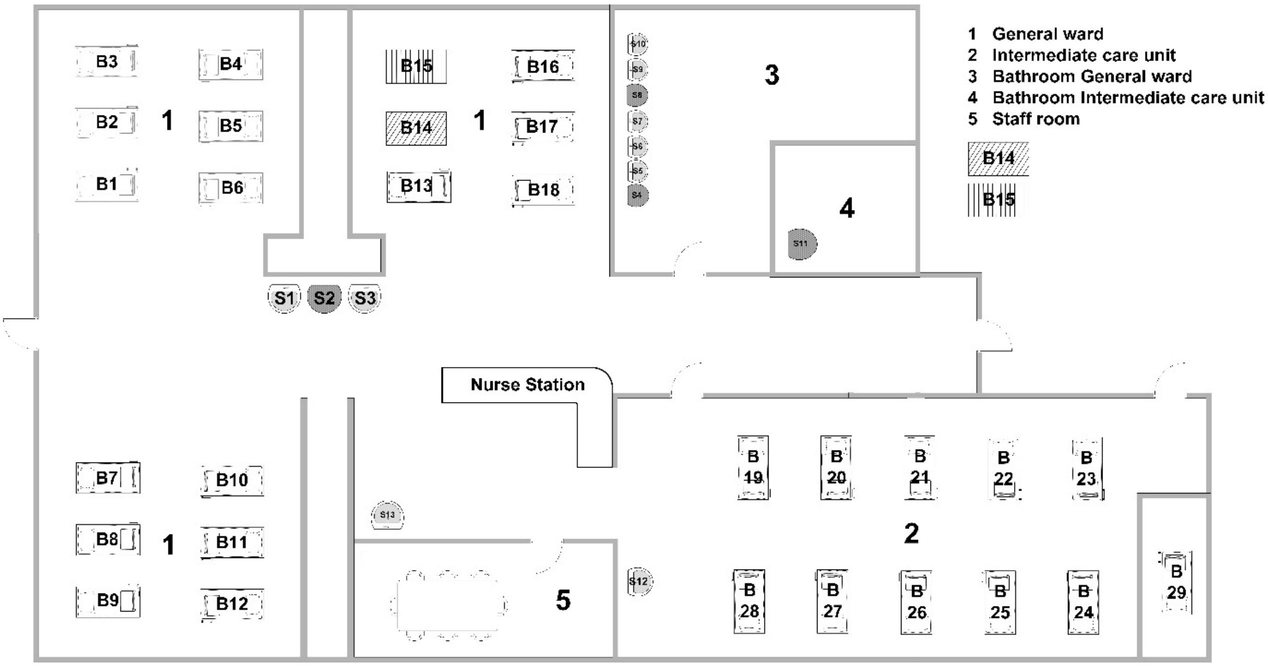

Figure 2. Room map of the general cardiovascular thoracic surgery and intermediate care units

Notes:

1. Patient A occupied bed 14 (hemocultures grew *P. aeruginosa* on July 11th, 2020) and patient B occupied bed 15 (hemocultures grew *P. aeruginosa* on July 18th, 2020)
2. Liquid soap above sink 2 (S2) grew *P. aeruginosa* > 100 CFU/mL
3. Liquid soap between S4 and S5 grew *P. aeruginosa* >100 CFU/mL
4. Liquid soap between S8 and S9 grew *Enterobacter cloacae* >100 CFU/mL, and *Klebsiella pneumoniae* >100 CFU/mL
5. Liquid soap between S4 and S5 grew *P. aeruginosa* >100 CFU/mL, and *Enterococcus faecalis* >100 CFU/mL

Table 1. Antibiotic susceptibility pattern of *P. aeruginosa* isolated from patients

Patient	Specimen	AMK	CPO	COL	CTZ	IMI	LFX	MEM	TAZ
A	Tip of CVC	S (<=8)	S (0.25)	I (2)	S (2)	S (2)	S (0.5)	S (<=0.5)	S (<=8)
A	Blood	S (<=8)	S (0.25)	I (2)	S (2)	I (4)	S (0.5)	S (<=0.5)	S (<=8)
A	Blood	S (<=8)	S (0.25)	I (2)	S (2)	I (4)	S (0.5)	S (<=0.5)	S (<=8)
B	Blood	S (<=8)	S (0.12)	I (2)	S (2)	S (2)	S (0.5)	S (<=0.5)	S (<=8)
B	Blood	S (<=8)	S (0.12)	I (2)	S (2)	S (2)	S (0.5)	S (<=0.5)	S (<=8)

AMK, amikacin; CPO, ciprofloxacin; COL, colistin; CTZ, ceftazidime; CVC, central venous catheter; IMI, imipenem; I, intermediate resistant; LFX, levofloxacin; MEM, meropenem; S, susceptible; TAZ, piperacillin/tazobactam

Table 2. Multilocus Sequence Typing (MLST) profile for *P. aeruginosa*

Samples	Allelic profile							Sequence type
	acsA	aroE	guaA	mutL	nuoD	ppsA	trpE	
Blood patient A	15	5	1	3	15	12	2	918
Tip CVC patient A	15	5	1	3	15	12	2	918
Blood patient B	11	2	6	3	15	38	3	3,393
Liquid soap	11	20	1	65	4	4	10	381
Liquid soap	11	20	1	65	4	4	10	381
Liquid soap	11	20	1	65	4	4	10	381
Liquid soap	11	20	1	65	4	4	10	381

CVC, central venous catheter

equipment. On one occasion, maximal sterile barrier was not followed. However, regarding catheter maintenance, the transparent dressings were changed regularly every 7 days, but were not changed when damp.

Cultures from various solutions in the units and operation theatres

Intravenous fluid and various solutions from the OR and from other hospital units were randomly sampled for bacterial cultures. The results are shown in Tables 3 and 4. The liquid soap used for hand washing in the general CVT surgery unit and the IMCU was commercial soap, brand A and brand B. Due to the viscosity of the commercial liquid soap, the patient support staff mixed the commercial soap with water to make it easier to wash out. They first transferred commercial liquid soap to a non-sterile container and mixing it with tap water, or water for irrigation without following a specific formula for the mixture and not recording the date of the mixture on the container labels.

DISCUSSION

We described 2 cases of *P. aeruginosa* BSIs which occurred in patients in the same surgical unit within 1 week. They were initially believed to

Table 3. Cultures from specimens in the intensive care unit, intermediate care unit, and general cardiothoracic surgical unit

Unit	Specimens	Culture result (CFU/mL)
ICU	4% alcoholic chlorhexidine	< 10
ICU	10% povidone-iodine	< 10
ICU	2% alcoholic chlorhexidine	< 10
IMCU	4% alcoholic chlorhexidine gluconate	< 10
IMCU	Liquid soap brand A	< 10
IMCU	Liquid soap brand A mixed with water for irrigation*	< 10
IMCU (bathroom)	Liquid soap brand B mixed with tap water*	2 specimens < 10 1 specimen grew *P. aeruginosa* > 100 and *Enterococcus faecalis* > 100
IMCU	10% povidone-iodine	< 10
IMCU	2% alcoholic chlorhexidine	< 10
General	Liquid soap brand B	< 10
General	Tap water (sinks 1-4)	4 specimens < 10
General	Liquid soap brand A mixed with hot water (sink 2)	4 specimens < 10 1 specimen grew *P. aeruginosa* > 100
General (bathroom)	Liquid soap brand B mixed with tap water (sink 4)	1 specimen grew *P. aeruginosa* > 100
General (bathroom)	Liquid soap brand B mixed with tap water (sink 8)	6 specimens < 10 1 specimen grew *P. aeruginosa* > 100 1 specimen grew *Enterobacter cloacae* complex >100 and *Klebsiella pneumoniae* > 100
General	Alcohol handrub	< 10
General	10% povidone-iodine	< 10
General	0.5% alcoholic chlorhexidine	< 10
General	2% alcoholic chlorhexidine	< 10
OR	NSS in bag	< 10
OR	LRS in a bag, soak ring, soak ring holder	< 10
OR	A solution from the cardiopulmonary bypass circuit	< 10
OR	Cardioplegia solution	< 10
OR	2% alcoholic chlorhexidine	< 10
OR	4% alcoholic chlorhexidine	< 10

CFR, colony-forming unit; ICU, intensive care unit; IMCU, intermediate care unit; OR, operating room
Note: There was no formula for mixing liquid soap with water, and no date of mixing labeled on the liquid soap bottle.

Table 4. Cultures from the heater-cooler of the cardiopulmonary bypass machine in the operating rooms

Operating room	Specimen	Culture result (CFU/mL)
A	Heater cooler 1	< 10
A	Heater cooler 2 before changing distilled water	*Cupriavidus pauculus* > 100
A	Heater cooler 2 after changing distilled water	*Sphingomonas paucimobilis* > 100 *Cupriavidus pauculus* > 100
A	Heater cooler 3 before changing distilled water	*Sphingomonas paucimobilis* > 100 *Cupriavidus pauculus* > 100
A	Heater cooler 3 after changing distilled water	*Cupriavidus pauculus* > 40
B	Heater cooler 1	< 10

be of the same clonality, triggering an outbreak investigation. Once *P. aeruginosa* was isolated from blood, we focused on an infused solution. Cultures of various solutions were then performed as part of this investigation. Initially, we hypothesized that there was potential for contamination of an infused solution used in the operating procedure or in the surgical field. However, we were unable to determine whether either the intravenous infusions or the solutions used in the operating procedures were contaminated as some of the solutions sampled for testing were not from the same lot as those used on the patients. The other hypothesis regarding the source of the infection was linked to the central line insertion and maintenance procedures. However, we failed to demonstrate contamination of skin antiseptic and normal saline solution (NSS) from the same lot used with the patients. Although *P. aeruginosa* was found in the cultures from the liquid soap in which the healthcare workers wash their hands, the MLST profile of isolates from patient A, patient B, and the liquid soap were different.

We did, however observe breaches in the hospital infection control practices, including the following:

1. Practices to prevent CLABSI were not strictly adhered to, in particular, the use of maximal sterile barriers and the replacement of dressings that are wet, soiled, or dislodged. Although the compliance rate was 93.3% for 15 observed catheter insertions, this rate may have been elevated due to the Hawthorne effect as during the observation, the surgical care team was aware of the two cases of BSIs.

2. The soap and water used for washing hands was unclean in many locations because the liquid soap was mixed with tap water to liquefy the mixture to make it less viscous, thus making it easier to wipe off.

3. The heater-cooler of the cardiopulmonary bypass (CPB) machine, although not directly related to the surgical area, was contaminated with bacteria that can inhabit water. The investigation revealed that the circuit had not been regularly maintained, mainly due to the COVID-19 pandemic, which restricted the operation and visiting of the hospital by people (including the staff performing the maintenance of the circuit).

The hospital administrative department responded immediately to the results of this investigation by revising the regulation for maintenance of the heater-cooler of the CPB machine and by supplying more appropriate materials, i.e., user-friendly liquid soap which does not need to be mixed with water, limiting the potential for contamination, making increased use of single-use towels, increasing emphasis on the systematic monitoring of adherence to prevention bundles, not only of CLABSI bundles but also bundles to prevent other hospital-acquired infections. In addition, as the culture of the tip of central venous catheter in patient A and the blood culture taken from peripheral veins were performed on the different days, we used the opportunity to emphasize appropriate blood collection for diagnosis of catheter-related bloodstream infection (CRBSI) to enable identification of the infection and to facilitate speedy, effective treatment.

These two cases were co-incident and were not epidemiologically linked, as they had different sequence types. In addition, during the investigation, four similar strains found in liquid soap used in the general CVT unit were different from those isolated from the patients in this study. This emphasizes the usefulness of molecular study to determine whether samples from different patients are caused by the same infectious agent. When conducting antibiotic susceptibility testing (DST) of *P. aeruginosa* isolated from the tip of CVC and blood from patient A, we noticed a one-dilution difference in the minimum inhibitory concentration (MIC) of the isolates to imipenem which raised the question of whether they were the same strain. The MLST confirmed the same clonality of isolates from patient A and distinguished it from that of patient B and the liquid soap. The MLST of liquid soap samples from various locations shown in Table 3 show similar sequence types. The contamination of liquid soap can occur during the preparation process prior to distribution to various locations.

Previous studies have found that *P. aeruginosa* can be prevalent in a hospital environment, occurring in potable water, faucets/taps, sinks, cleansing equipment, and hydrotherapy equipment (1). It can also colonize liquid antiseptics, e.g., quaternary ammonium compounds, infusion fluids and soap solutions, and can be transmitted causing infections in hospitalized patients (2-7). These bacteria can form biofilms which make them resistant to antibiotics and which allow them to adhere to catheters (1, 8). *P. aeruginosa* is a significant pathogen among hospital-acquired infections and can cause morbidity and mortality, particularly in the case of multidrug-resistant strains (9). However, acknowledgment of this being a hospital-acquired pathogen enabled the hospital to improve measures to avoid infection despite it not having been an actual outbreak. It motivated taking action to identify potential reservoirs and modes of transmission to help prevent future outbreaks.

One may question whether in this case it was too early to start an outbreak investigation as those two cases may have occurred by chance and an outbreak investigation results in the loss of hospital resources. However, in the authors' point of view, the definition of an outbreak was met, i.e., an increase in the disease incidence beyond the expected number of cases in a particular area within a defined period of time (10). In addition, if there really was a reservoir, it would be harmful to patients, particularly those undergoing cardiac valvular surgery and who then develop prosthetic valve endocarditis. In such a case, the outcome could be devastating, both from the perspective of the patient and from that of the hospital. In general, any outbreak is an emergency condition and stopping it early can potentially limit the impact and the number of cases involved.

The major limitation of this investigation was that the specimens were prospectively collected only after the two cases had been detected. As a result, some of the solutions sampled for testing were not from the same batch as those used on the patients. Therefore, the negative culture results obtained from these samples as a source of infection cannot be completely excluded.

CONCLUSIONS

We present two unlinked cases of *P. aeruginosa* bloodstream infection along with contamination of liquid soap with *P. aeruginosa*. Although this was not an actual outbreak, investigation of these two cases uncovered breaches in infection control practices and provided an opportunity to improve the infection control strategies in our institution.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

Conceptualization, R.C.; methodology, R.C., A.G.; investigation, N.N., A.G., P.K., S.K., U.T.; data curation, N.N., A.G.; writing—original draft preparation, N.N., R.C.; original draft preparation, review and editing, R.C.; supervision, A.P.; funding acquisition, R.C.

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