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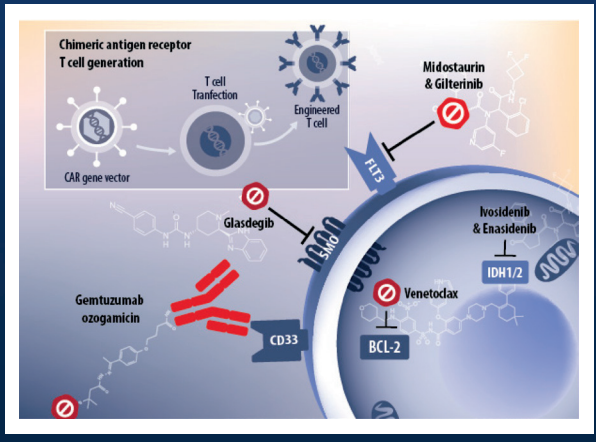
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The Effectiveness of Computer-Assisted Instruction for Caring Nasogastric Tube: a Randomized Controlled Study

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ABSTRACT

Objective: To compare the effectiveness of Computer-Assisted Instruction (CAI) with traditional instruction for the training of nurse assistant students in the care of patients with nasogastric tube (NG tube).

Methods: Nurse assistant students were randomized to either the CAI group or the control group. Student academic performances, including both the theoretical and practical parts were observed.

Results: 170 participants were enrolled in this study and were equally randomized to CAI group (n=85) and the control group (n=85). 24.7% of CAI group (24/85) and 14.1% of control group (12/85) passed both examinations (Difference 10.6% (95% CI: -1.37% to 22.57%), $p = 0.081$). Interestingly, 54.1% of the CAI group whereas only 35.3% of the control group passed the theoretical part examination (Difference 18.8% (95% CI: 3.8% to 33.0%, $p = 0.041$). For practical part, 64.7% of the CAI group and 58.8% of the control group passed the examination (Difference 5.9% (95% CI: -8.73% to 20.26%, $p = 0.430$).

Conclusion: For nurse assistant students, CAI for caring the patients with NG tube did not demonstrate benefit for the whole examination. However, CAI seemed to offer some benefit for teaching especially the theoretical part.

Keywords: A randomized controlled trial; computer-assisted instruction; nurse assistant students; patients with nasogastric tube (Siriraj Med J 2019; 71: 324-330)

INTRODUCTION

Students enrolled at the School of Nurse Assistant Siriraj Hospital endeavor to develop their ability to become productive, contributing, and essential members of the total healthcare experience team at Siriraj Hospital. Creativity, critical thinking, communication, and collaboration are essential components of an effective educational program.[1] Theoretical and practical medical education at all levels is necessary for providing effective care and treatment and to assist in preventing healthcare-related errors and omissions. Care of patients with nasogastric tube (NG tube) is a key responsibility of nurse assistants. Instruction given to nurse assistants in NG tube-related patient care protocols is generally delivered via textbooks and lectures in a traditional classroom setting. Though NG tube-related care involves gastric intubation, enteral tube feeding, NG tube cleaning, and NG tube removal, nurse assistant students receive only one combined theoretical and practical course in NG tube-related care. This abbreviated training in NG tube-related care may lead to complications in NG tube management, unprofessional techniques, and negative physical and psychological outcomes for patients. Accordingly, the inclusion of computer-assisted instruction (CAI) as

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a method for training nurse assistants in the care of patients with NG tube may yield significant benefits for both our patients and our center.

The ongoing development of technology continues to provide additional and often improved methods for supporting instructors. Dedicated computer-assisted instruction (CAI) modules have been created to help teach nurse assistants the theories and methods used in the care of patients with NG tube. Specifically, CAI involves learning via computer using specifically designed software. Several educational computer programs are available online, from computer stores, and from textbook publishing companies. These instructional software packages offer several instructional enhancements, including well-produced animation, sound, and visualized and detailed demonstration. Using these programs, students are able to progress at their own pace and work individually. After receiving instruction, students can form groups and engage in the solving of hypothetical clinical NG tube-related problems. Another benefit of CAI is that these programs often provide immediate feedback, letting students know whether their answer is correct or not.[2] CAI also improves instruction for students with disabilities, making access to instruction easier and more convenient. CAI has the ability to capture student attention for the following reasons: instructional software programs are interactive and interesting, programs are designed to engage the student's spirit of competitiveness to increase scores, and computers are fundamental to a student's digital world experience. Another advantage of CAI is that it moves at the student's pace and normally does not move ahead until the student has mastered the skill being taught. Programs also provide differentiated lessons to challenge students who are at-risk, average, or advanced.[2-3] Demonstrated advantages of active learning, reflective learning, independent learning, and task-based teaching were all observed in students who learned using CAI.[4]

Computer-assisted instruction (CAI) was investigated in this study to determine if it is a better instruction method than traditional class-based instruction for nurse assistant training in the care of patients with NG tube at the School of Nurse Assistant Siriraj Hospital.

MATERIALS AND METHODS

This experimental study was conducted among students enrolled at the School of Nurse Assistant Siriraj Hospital, a subsidiary unit of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Inclusion criteria were nurse assistant students who were enrolled in SIPN 043-NG Tube Healthcare course and who were older than 18 years of age. Students were excluded if they were for some reason unable to participate in or follow the protocol of the study. The study design was a randomized controlled trial. One hundred and seventy nurse assistant students were enrolled in this study, of which 85 were randomly assigned to the computer-assisted instruction group (CAI group) and 85 were allocated to the PowerPoint instruction group (control group). Study group randomization was determined by computerized randomization. Student age, GPA, and O-net (Ordinary National Educational Test) scores were not different between groups (Table 1).

TABLE 1. Demographic and academic performance data of 170 nurse assistant students.

Data	Sample	
	CAI Group (n=85)	Control Group (n=85)
Gender		
Male	7 (8.2%)	3 (3.5%)
Female	78 (91.8%)	82 (96.5%)
Age (yrs)	19.2±1.3	19.3±1.3
GPA	3.1±0.4	3.1±0.4
O-Net score	179.8±16.8	179.6±15.5
Anatomy and physiology score	41.5±7.5	41.8±7.2

Data are presented as n (%) or mean ± standard deviation

The hypothesis of our study comprised a primary and a secondary outcome. Instructor's teaching and outcome experience found that 60% of students passed both the theory and practical skills course components with a score >70%. As such, the primary outcome hypothesis was that >80% of the students in the CAI group would pass both components of the exam with a score of 20 for theory and 11 for practical skills or higher. According to a calculation by nQuery Advisor software (Statistical Solutions Ltd., Cork, Ireland), a *p*-value = 0.05 was calculated using a 2-sided test ($Z_{\alpha}=Z_{(0.05/2)}=1.96$) and a power = 80% ($Z_{1-\beta}=Z_{0.8}=0.84$). The secondary outcome hypothesis was that >70% of students in the CAI group would report satisfaction with computer-based learning in order to compare students behavior during studying of media learning between CAI and control groups such as motivation, interest in lesson and cooperative learning. Data were collected from 6 October 2014 to 9 October 2014. The student instruction and data collection process for each day of the training was conducted, as follows:

Day 1: All students in both study groups attended traditional lecture-based instruction in NG tube-related patient care protocols in a traditional classroom setting.

Day 2: Students were randomly separated into the 2 study groups for lecture review. The control group was provided with a textbook and PowerPoint instruction and the CAI group was provided with computer-assisted instruction (CAI). The duration of the review and study period was 3 hours, with student study behavior observed and recorded by School of Nurse Assistant Siriraj Hospital's staff.

Day 3: A 25 question multiple-choice examination was given to students in both groups to test their knowledge. The same exam was given to both groups.

Day 4: A practical examination consisting of 16 operations on a medical model was given to students in both study groups. Enteral feeding exam was also given to both groups on day 4.

Data were analyzed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are presented as mean ($\overline{X}$) ± standard deviation (SD). Student examination scores were analyzed by chi-square test, with results presented as odds ratio (OR) and 95% confidence interval (CI). A *p*-value<0.05 was considered statistically significant (Tables 2-3).

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital (Si 429/2015). CAI instructional content was reviewed and approved by 3 experts by report evaluation and instructional content validity was verified by the course instructor.

TABLE 2. Knowledge and practice skill scores for lesson on patient with NG tube health care (n=170).

Score	Sample		Mean difference (95% CI)	*P*-value
	CAI Group (n=85) (mean±SD)	Control Group (n=85) (mean±SD)		
Knowledge score	18.1±2.4	16±3.0	2.1 (1.3 - 2.9)	<0.001
Practice skill score	20.9±4.6	20.6±5.0	0.3 (-1.2 - 1.7)	0.735

A *p*-value<0.05 indicates statistical significance

TABLE 3. Pass rates by type of assessment for CAI and control groups.

Type of assessment	CAI Group (n=85) n (%)	Control Group (n=85) n (%)	Difference (95% CI)	*P*-value
Pass theory	46 (54.1)	30 (35.3)	18.8% (3.8% - 33.0%)	.041
Pass practice skill	55 (64.7)	50 (58.8)	5.9% (-8.73% - 20.26%)	.430
Pass theory and practice skill	21 (24.7)	12 (14.1)	10.6% (-1.37% - 22.57%)	.081

A *p*-value<0.05 indicates statistical significance

RESULTS

A total of 170 students were enrolled, with students randomly allocated into one of two study groups [CAI group (n=85) or control group (n=85)]. There were no exclusions and all enrolled participants were analyzed (Fig 1). Objective testing results for subject theory were statistically significantly higher in the CAI group than in the control group (18.1 vs. 16) (p<0.001, T-test) with mean difference equal to 2.1 (95% CI; 1.3-2.9). Scores for the practical examination were only slightly higher in the CAI group than in the control group, with the difference failing to achieve statistical significance (20.9 vs. 20.6) (p=0.735, T-test) (Table 2).

The procedure for enteral feeding of patients with NG tube was important for students to carefully follow - particularly 2 key points. The students were required to position the patient with the head at a 30-45 degree angle and drain gastric content for purposes of testing the position of the feeding tube. A failure to perform these two key steps resulted in a failing grade for the practical component of the test. Regarding the 25 question multiple-choice examination, the CAI group performed significantly better than the control group (46 *vs.* 30) (p=0.041, Chi-square). The level of passing scores for the practical examination were not significantly different between groups (55 *vs.* 50) (p=0.430, Chi-square). Pass rates by type of assessment for CAI and control groups are presented in Table 3. Regarding the number of students that passed both the theoretical and practical portions of the exam, the CAI group exceeded the control group by 10% (21 *vs.* 12) (p=0.081, Chi-square).

Student levels of satisfaction regarding different aspects of computer-assisted instruction (CAI) are shown in Table 4. Mean level of student satisfaction with CAI was 4.58 out of 5. Nine students (10.6%) commented that CAI was "modern", "easy to understand", "colorful", and "exciting to learn". Regarding other feedback results, 7.65% of students requested that CAI be used for instruction in other lessons, 2.55% said they would like to have more available exercises, and 1.7% indicated a desire to have the ability to study at home with CAI. Eight students (9.4%) expressed displeasure that the playback button was necessary in the exercise section. Regarding student behavior during the study period, students in the control group demonstrated a low level of attention and minimal active learning behavior. In contrast, the CAI group demonstrated much higher levels of attentiveness during the study period (Table 5).

DISCUSSION

Our null hypothesis in this study (primary outcome: Theoretical instruction pass rate of >80% and practical instruction pass rate of >70%) was not able to be rejected based on the combined pass rate (theory and practical) in

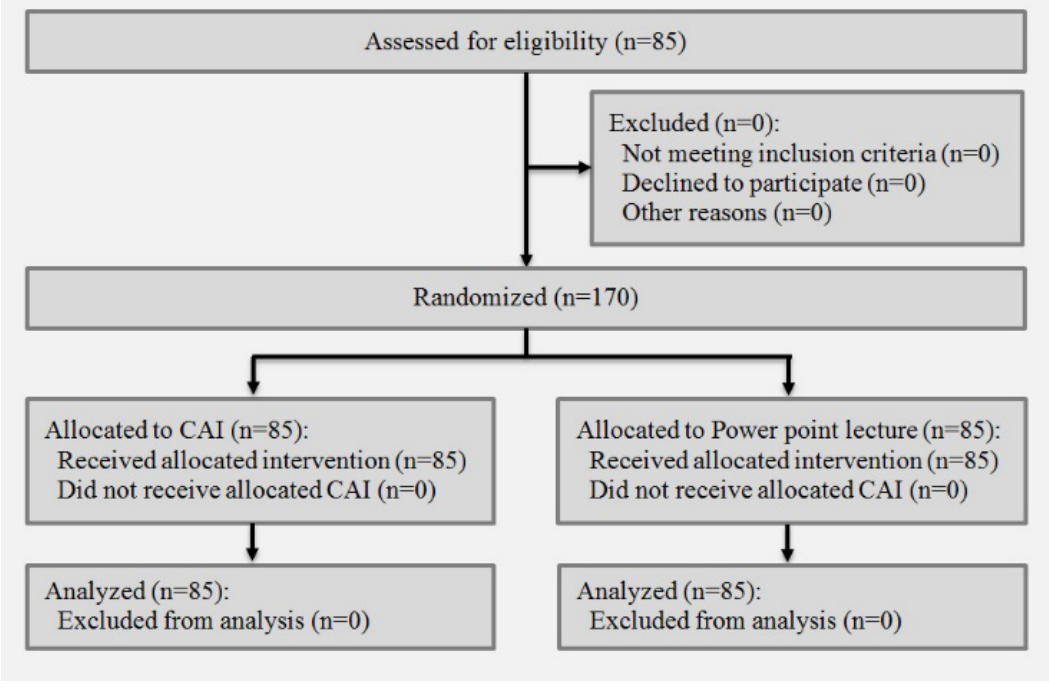


Fig 1. Flow diagram of participant eligibility and randomization process.

TABLE 4. Student level of satisfaction with computer-assisted instruction (CAI) (n=58).

Topic	Level of satisfaction Mean±SD
Total for content presentation	4.57±0.12
Presentation easy to understand	4.67±0.52
Language easy to understand	4.64±0.61
Appropriateness of lesson sequence	4.64±0.55
Appropriateness of lesson content difficulty	4.48±0.65
Appropriateness of number of exercises in the lesson	4.40±0.76
Total for design of learning media	4.39±0.20
Convenient use of button	4.05±0.98
Composition of media learning appropriate and interesting	4.48±0.68
Appropriateness and clarity of characters	4.58±0.62
Appropriateness of sound effects	4.40±0.90
Ability of media learning to motivate students	4.45±0.76
Total for lesson satisfaction	4.65±0.06
Students are attentive and enjoy the lesson	4.58±0.59
Students find the answer by themselves and can repeat the lesson	4.62±0.62
Students are satisfied with the outcome of the lesson	4.62±0.53
Students can easily study by themselves	4.66±0.52
Students can study independently	4.75±0.46
Overall total	4.53±0.17

TABLE 5. Student learning behavior in the CAI and control groups.

Behavior	CAI Group (n=85)	Control Group (n=85)
Display interest in and attention to media learning	Students display interest in and pay attention to media learning and ask staff when they have a question	Students do not pay attention to or display interest in media learning; students look tired and unmotivated Half of students watch another video that is not related to the lesson
Behavior during media learning	Some students talk to each other, but most pay attention to media learning Some students reset their lesson to repeat again	Students play on their mobile telephones, talk to each other, sleep, and/or wait for the time they can leave the room
Behavior after media learning	Students cooperate with each other to answer questionnaire Some students ask their friends about the lesson and how to use media learning	Students continue to display a lack of interest in learning Some students remain attentive to their lesson as their friends leave the room

the study group of only 24.7%. Students became nervous during the examination, causing them to demonstrate incorrect process of nursing care. Although most students knew the related processes, a loss of concentration and test anxiety adversely affected their scores. Previous study of the effects of instructional videos on knowledge and practical skills of labor and delivery nursing students demonstrated that these learning materials were useful in improving student knowledge in clinical practice during the intra partum period.[5] Similar to the results of a comparative study on the effectiveness of two teaching medias: use of video and use of flip chart instructions on the knowledge of postpartum woman, the video group in this study had higher practicum and satisfaction scores than those of the control group.[6] However, one-time use of CAI for students to practice their NG tube healthcare skills could not improve student skills in this study. As suggested by several opinions, students require several learning and practice opportunities, including repeated demonstrations, before they should be asked to perform a skill.[3,7] A study that used CAI to enhance student critical thinking ability found a difference in knowledge scores between pre-test and post-test scores, but there was no difference in critical thinking skills.[8,9] Exposing students to new types of CAI has been proposed.

Park EJ found computer-assisted instruction (CAI) was likely to be useful and practical in the training of abstract skills to nursing students, though certain challenges remain, such as the precise understanding of cognitive or affective responses to ethical issues.[10] Their finding suggests effective use of the constructivist learning theory, which actively emphasizes students as the key factor in improving learning outcomes. The variability in teaching levels and instructional resources that are available via CAI enables students to develop knowledge and skills and construct meaning according to his/her preferred style of learning. Attractive and eye-catching colors, endearing animated characters, music and sound effects, and compelling visual effects and animation effectively attract student attention and create a fun and relaxed learning atmosphere. CAI methods can achieve excellent results, with students' reading and speaking abilities being continuously enhanced during the learning process.[11]

There is limited empirical evidence regarding the effectiveness of CAI in clinical skills education.[12] A previous study in Information and Communication Technologies (ICTs) found many obstacles to CAI nursing education.[11] They reported age, previous knowledge, and preferred learning style as factors that affected learning of nursing clinical skills. They also recommended the following research guidelines for studies investigating CAI instruction: randomized controlled trial study design, avoid voluntary recruitment, and test for differences in the demographic characteristics of participants in the study groups.

The results of this study revealed computer-assisted instruction (CAI) to be useful in improving student knowledge, but not in improving student practical skills. In addition to instruction by CAI, demonstration of practical skills by the instructor is required to improve student practical skills. Based on the promising findings of this study, the authors recommend the integration of CAI as an instruction method for students at the School of Nurse Assistant Siriraj Hospital. Integration should include other nursing care training subjects and the use of pre-test and post-test to evaluate training effectiveness. Moreover, the results of this study should inform teachers of nurses and nurse assistants not only to confidently incorporate CAI for teaching theoretical parts but also to build more "real skill" training with patients in practical part.

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DIR/Floortime® Parent Training Intervention for Children with Developmental Disabilities: a Randomized Controlled Trial

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ABSTRACT

Objective: To determine whether adding a parent training program utilizing the Developmental Individual-difference Relationship-based (DIR/Floortime®) approach for children with developmental disabilities can improve their capacities for attention and initiation.

Methods: Forty-eight pairs of parents and their preschool children with developmental disabilities were randomly assigned to three 1-hour one on one DIR/Floortime® parent training sessions during a 4-month period or to a control group.

Results: Between-group comparison demonstrated a significant difference in favor of the intervention group for attention ($F(1, 46) = 34.52$, $p = .031$, $ph^2 = .099$) and initiation composite scores ($F(1, 46) = 6.55$, $p = .014$, $ph^2 = .127$). Effect sizes were medium to large for the attention composite score (Cohen's $d = .526$) and initiation composite score (Cohen's $d = .653$) respectively.

Conclusion: Adding a modest home-based DIR/Floortime® parent training approach may yield clinically meaningful improvements in attention and initiation for children with a range of developmental challenges.

Keywords: Child development; developmental disability; parent training; DIR/Floortime® (Siriraj Med J 2019; 71: 331-338)

INTRODUCTION

Children with non-autistic developmental disabilities typically exhibit challenging limitations in self-care and are at high risk of developing emotional and behavioral problems compared to typically developing children.[1-3] Studies of parent training for children with developmental disabilities are promising.[4-7] There is good evidence that parent training can yield increased positive parenting and reduction in problematic behaviors in children. These approaches utilize contingency management, planned activities, compliance training, or a combination of these. Some emphasize the importance of fostering more positive relationships between parents and children.[8-13] These strategies, however, are designed to be applied in a generalized manner without explicitly taking into account the neurological and developmental capacities of individual children.

The Developmental Individual-differences Relationship-based (DIR)/Floortime® model[14] focuses on the child's developmental capacity for relating and communicating, taking in, regulating, responding, understanding sensations and information, and planning actions. It is a developmental intervention involving meeting a child at his or her current developmental level, in which the parent or therapist

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follows the child's lead, with playful positive attention while tuning into the child's interests. Once the child connects with the adult, specific techniques are used to challenge and entice the child to move toward ever more complex developmental milestones outlined in the DIR model. In DIR/Floortime® relationships are the pivotal force that nurtures and optimizes development. DIR/Floortime® parent training can improve the core challenges of autism, including relating, interacting, and communicating.[15-17]

Prior to this study, most research on DIR has focused on investigating the effectiveness of DIR/Floortime® in the children with ASD. It has been less clear whether DIR might help children with developmental disabilities who generally have better social abilities than children with ASD.[18-20] It would, therefore, be helpful to learn whether DIR might help other vulnerable populations.

This study seeks to determine whether DIR/Floortime® parent training program for children with development disabilities confers benefit beyond treatment as usual (TAU).

MATERIALS AND METHODS

Study design and participants

After the Institutional Review Board of Faculty of Medicine Siriraj Hospital, Mahidol University approved this study (Si 089/2013), caregivers (parents, or an adult in a caregiving role) were recruited through posters and paper advertising from February 2013 to December 2016. One of the researchers who was a developmental pediatrician confirmed the diagnosis. Inclusion criteria included: patient: diagnosed with a developmental disability, global developmental delay, or a cerebral palsy; age 2 to 6 years; and living with the caregiver for at least 6 months. Children with co-occurring ASD, significant impairments in hearing or vision serious medical problems, intractable seizures, and those whose caregivers were illiterate were excluded.

After the participants agreed and signed informed consent and had undergone a baseline assessment, the children were sorted into 2 strata according to age (24-47 or 48-72 months).

The study is a single-blind, parallel design clinical trial with an allocation ratio of 1: 1. A research assistant who was not directly involved with the study used a random number table to randomly allocate participants to either the DIR/Floortime® parent training group or a waitlist control group. Opaque envelopes were used to conceal the allocation sequence.

Intervention

Treatment was carried out using the DIR/Floortime®[14] approach. The first author was an experienced clinician who had her expert training leader certification from the Interdisciplinary Council on Developmental and Learning Disorders. Caregivers in the intervention group viewed a 2-hour DVD about DIR/Floortime® and received an accompanying book, an approach previously utilized to study the method with parents of children with ASD.[16,21]

Caregivers were trained for 1 hour on how to observe their children's cues and responses. Caregivers were coached to join the children in pleasurable activities, maintain engagement, and to sustain reciprocal interactions. For children with symbolic capacity, pretend play was encouraged. Controlling and intrusive responses on the part of caregivers were identified, discouraged, and substituted with two-way emotional gestural communication.

Caregivers in the intervention group were asked to spend a minimum of 15 hours per week utilizing DIR/Floortime® techniques throughout the study period. Parents of the children in both groups were asked to continue their other usual treatment interventions such as physical therapy or speech therapy throughout the study period. At the end of the first and third months, the researcher observed and gave feedback to parents in the intervention group about how well they were related to their children. The assessment was based on the child and caregiver's functional emotional capacities.[22] Controlling and intrusive responses were again identified and discouraged and substituted with responses aimed at facilitating two-way emotional signaling and communication between parents and their children. Modeling and coaching were used to improve caregiver performance. The goals, method, and techniques of home program were adjusted to meet the child's current needs. Both groups were reassessed at the end of the fourth month.

Measurements

Baseline measurement included assessment of the children's development and family demographic characteristics.

Child Behavior Rating Scale (CRBS)

The CBRS[23] was the primary outcome measurement, rating the children's interactions with their caregivers. The caregiver and child were video-recorded while playing together in any manner they chose. The assessors were two developmental psychologists who were blinded to the group status. They rated Attention (attention to activity, persistence, involvement, and compliance or cooperation subscales), and Initiation (initiation of activity, joint attention, and affect). The assessors rated each of the items on a 5-point Likert scale. The two

assessors' scores were averaged and subscale scores were averaged for composite scores. Cronbach's alpha for the two assessors was 0.94 for the attention composite score and 0.77 for initiation.

Functional Emotional Developmental Questionnaire (FEDQ)

The FEDQ[24] is a questionnaire for the parent to assess Greenspan's six Functional Emotional Developmental Levels (FEDLs): (1) shared attention and regulation, (2) engagement and relating, (3) purposeful emotional interaction, (4) social problem-solving, (5) creating ideas, and (6) logical use of symbolic ideas in social problem solving. All are scored on a 7-point scale. The Thai version of the FEDQ has a satisfactory internal consistency (Cronbach's alpha = 0.83) with an ICC of 0.89.[25]

Mullen Scales of Early Learning (MSEL)

The MSEL[26] is a developmental test for children from birth to 68 months of age. Four cognitive domains of the MSEL were used: visual reception, fine motor skills, receptive language, and expressive language. This instrument was administered by a developmental pediatrician who was blinded to intervention status. Subscale scores are compared against age equivalents and summarized as the Early Learning Composite (ELC). Higher scores reflect more intact development.

Parenting Stress Index-Short Form (PSI-SF)

The PSI –SF[27] is a 36-item questionnaire designed to measure stress in the parent-child system on three subscales: parental distress, parent-child dysfunctional interaction, and difficult child. Higher scores indicate greater stress. The ICC of the total Parenting Stress Index score in the current study was 0.82.

Compliance and co-interventions

Parents kept logs of hours per week they used DIR/Floortime® technique as well as other interventions.

Sample size calculation

A prior study found a mean CBRS score (initiation) of 2.8 [standard deviation (SD), 0.9] for a population of children with developmental disorders other than autism.[23] In the present study, we sought to detect a minimum clinically important between-group difference of 0.8. A sample size of 40 was needed to provide 80% power to detect this difference at a two-tailed significance level of 0.05. If the estimated drop-out rate was 20%, the number of subjects to be recruited was 48.

Data analysis

Data were analyzed using SPSS, version 18.0. An intent-to-treat analysis was used. For drop-outs, we used the last-observation-carried-forward method. Paired t-tests compared pre-test and post-test scores. Analysis of covariance was conducted to investigate the impact of the treatment intervention between groups, with follow-up scores as the dependent measure and baseline scores as covariates.

RESULTS

Sixty families were screened: 4 declined to participate, 2 did not respond to the baseline evaluation, and 6 were not eligible because of the children's health problems. Forty-eight families were randomized to either the treatment group (n = 23) or control (n = 25). Six families dropped out, 3 from each group. Reasons included an inability to reach the caregivers, moving away, and 'too busy'. (Fig 1)

The average age of the children was 39.98 months. Sixty-eight percent of the diagnosis was global developmental delay. Most were living in a two-parent household. Seventy-five percent had an ELC of ≤50, indicating moderate to severe developmental delay. Eighty-five percent received usual services averaging 1.14 hours per week. Groups did not significantly differ concerning for average service hours. The parent and child demographic characteristics were not significantly different between groups (Table 1). We used intention to treat analysis and the last-observation-carried-forward method for missing data.

Primary outcome

Control group post-test attention and initiation composite scores of the CRBS were not significantly different from pre-test scores. Intervention group post-test attention and initiation composite scores were significantly higher than pre-test scores ($p < .001$). Between-group comparison demonstrated a significant difference in favor of the intervention group for attention ($F(1, 46) = 34.52$, $p = .031$, $p\eta^2 = .099$) and initiation composite scores ($F(1, 46) = 6.55$, $p = .014$, $p\eta^2 = .127$). Effect size for the difference between groups was medium to large for both the attention composite score (Cohen's $d = .526$) and initiation composite score (Cohen's $d = .653$) (Table 2).

Subscale results demonstrated significantly better outcomes for the persistence, involvement, initiation of activity, and joint attention subscales. There were no significant differences in attention to activity, compliance, or affect (Table 2).

TABLE 1. Demographic information and statistical tests of group differences for participants.

	Control group N=25	Intervention group N=23	*P* value
The children			
Mean (SD) age in months	39.36 (11.4)	40.65 (13.6)	.301
Male	11 (44%)	14 (56%)	.243
Diagnosis			
Down syndrome	2 (8%)	4 (17%)	
Cerebral Palsy	7 (28%)	7 (30%)	.561
Global developmental delay	16 (64%)	12 (52%)	
Mean (SD) CBRS			
Attention composite scores	3.04 (0.90)	2.85 (0.93)	.473
Initiation composite scores	2.91 (0.77)	2.53 (0.77)	.096
Mean (SD) FDQ	32.24 (11.21)	29.61 (11.03)	.564
Early Learning Composite			
More than 85	3 (12%)	2 (9%)	
71-85	4 (16%)	1 (4%)	.538
50-70	7 (28%)	9 (39%)	
Less than 50	11 (44%)	11 (48%)	
History of convulsion	1 (4%)	2 (9%)	.532
Participation in daycare or kindergarten	5 (20%)	7 (30%)	.617
Their families			
Primary caregiver:			
Parent / Grandparent	19 (76%)/ 6 (24%)	15 (65%)/ 8 (35%)	.412
Bachelor degree or higher	11 (44%)	6 (26%)	.195
Two-parent household	22 (88%)	20 (87%)	.195
Worked inside of the home	14 (56%)	11 (48%)	.466
Sibling in family (yes/ no)	19 (76%)	20 (87%)	.571
Mean (*SD*) Total PSI score	87.88 (21.09)	93.52 (27.5)	.390

Secondary outcomes

Intervention group post-test FEDQ scores were significantly higher than the pre-test score ($p = .001$) but not significant in the control group ($p = .099$). Between-group analysis revealed significant differences in favor of the invention ($F(1, 46) = 7.37$, $p = .031$, $p\eta^2 = .141$). The effect size for the difference between groups was medium to large (Cohen's $d = .729$).

For both groups, post-test MSEL subscale scores were significantly higher than the pre-test scores. Between-group analysis showed that the invention group had significantly better scores for the receptive language

TABLE 2. Presents mean (SD) of the outcome measures and the results of the analysis of covariance (ANCOVA) for group analyses.

	Control Group (n=25)		Intervention Group (n=23)		F (1, 46)	*P* value	Cohen's *d*
	Pre-test	Post-test	Pre-test	Post-test			
Child Behavior Rating Scale (CBRS): Attention Domain							
Attention to Activity	3.40 (1.00)	3.44 (1.12)	3.21 (1.08)	3.54 (0.91)	2.12	.153	.421
Persistence	2.80 (0.92)	3.04 (0.97)	2.61 (1.08)	3.19 (1.03)	4.21	.046*	.574
Involvement	3.02 (1.04)	3.24 (1.01)	2.83 (0.94)	3.48 (0.74)	4.95	.031*	.570
Compliance	2.92 (0.98)	3.02 (0.94)	2.74 (0.94)	2.96 (0.94)	0.18	.671	.116
Attention composite scores	3.04 (0.90)	3.18 (3.29)	2.85 (0.93)	3.29 (0.79)	4.94	.031*	.526
Child Behavior Rating Scale (CBRS): Initiation Domain							
Initiation to activity	2.80 (1.00)	2.84 (1.04)	2.26 (0.93)	2.87 (0.98)	11.99	.009	.944
Affect	2.62 (0.83)	2.82 (1.06)	2.43 (0.83)	3.00 (0.87)	3.35	.074	.527
Joint attention	3.30 (0.93)	3.34 (0.85)	2.89 (0.80)	3.30 (0.78)	4.91	.032*	.443
Initiation composite scores	2.91 (0.77)	3.30 (0.86)	2.53 (0.77)	3.06 (0.77)	6.55	.014*	.653
Total FEDQ Score	32.24 (11.21)	33.76 (11.81)	29.61 (11.03)	37.35 (11.37)	7.37	.009*	.729
Mullen Scales of Early Learning (MSEL)							
Visual Reception	23.68 (9.26)	26.04 (9.57)	20.91 (11.9)	25.35 (11.31)	1.97	.167	.648
Fine Motor	21.64 (7.41)	23.80 (8.03)	20.48 (8.12)	22.91 (8.91)	0.079	.780	.170
Receptive Language	21.56 (8.89)	22.92 (9.45)	19.17 (10.33)	23.55 (11.15)	4.33	.043*	.663
Expressive Language	17.64 (10.69)	18.68 (9.45)	15.39 (9.85)	18.90 (9.85)	5.53	.023*	1.11
Parental Stress Index							
Parental Distress	30.08 (8.92)	29.04 (7.20)	31.43 (10.6)	29.09 (9.83)	0.148	.702	.140
Parent-Child Dysfunctional Interaction	29.72 (6.10)	28.64 (6.96)	28.09 (8.28)	32.00 (7.98)	5.27	.026*	.414
Difficult Child	29.16 (8.89)	28.6 (8.16)	30.74 (9.82)	30.09 (9.12)	0.237	.629	.112
Total Parental Stress Index	87.88 (21.09)	85.30 (24.28)	93.52 (23.98)	85.03 (24.29)	1.240	.271	.275

* p value < 0.05

subscale ($F(1, 46) = 1.97$, $p = .043$, $p\eta^2 = .088$) and the expressive language subscale ($F(1, 46) = 1.97$, $p = .043$, $p\eta^2 = .109$). There was no significant difference in the visual reception or fine motor subscales. Mean changes in the ELC score in this study could not be calculated because scores were lower than 49.

Intervention group PSI-SF post-test parent–child dysfunctional interaction score was significantly lower than pre-test ($p = .011$). Parental stress and difficult child scores did not significantly change from baseline. Between-group analysis showed that the parent–child dysfunctional interaction score in the intervention group was the only individual subscale score that was significantly higher than that in the control group when the pre-test score was a covariate ($F(1, 46) = 5.27$, $p = .026$, $p\eta^2 = .033$). No other adverse effects of the intervention were detected.

Moderator analysis

Regression analysis was carried out to determine the moderator effect of baseline variables on the improvements in the attention and initiation composite scores. Age, groups of children classified by ELC, and baseline score demonstrated some association with the improvement in the attention ($R^2 = .284$, $F(3, 44) = 5.83$, $p = .002$) and initiation composite scores ($R^2 = .381$, $F(3, 44) = 5.83$, $p = .001$). Pre-test attention and initiation composite scores had a significant negative weight, indicating the children with higher baseline scores might have a lower chance of improving. Age of the children was significantly associated with the improvement in initiation composite scores, i.e., older children were more likely to show improved initiation. Pre-test ELC did not demonstrate moderator effect on both composite scores.

Compliance and co-interventions

35% of the intervention group reported using DIR/Floortime® techniques an average of 14 hours/week; 52% spent 7 to 14 hours/week; 13% spent <7 hours/week. Children in both the control and intervention groups received additional services (e.g., speech therapy, occupational therapy, or physical therapy) for an average of 1.20 (SD, 0.58) hours/week and 1.08 (SD, 0.73) hours/week, respectively. There were no significant differences in the time spent receiving such services between the two groups ($p = .554$).

DISCUSSION

This study supports the feasibility of studying DIR/Floortime® parent training intervention across groups of children beyond those with autism.[15-17,28] Children with non-autistic developmental disorders in the intervention group showed significantly greater involvement and had better communication with their parents or caregivers. Effect sizes were medium to large. The lack of significance in CBRS changes in compliance or cooperation and attention to activity scores between groups is similar to Casenhiser.[17] However, DIR/Floortime® does not focus on compliance nor activity but on encouraging initiation and interaction.

In this research protocol, we asked parents to spend at least 15 hours per week using the intervention with their children. Parent logs showed that only one-third of parents met the requested time. The studies of parent training programs found that when the programs were implemented with high fidelity, the parenting practices improved significantly, but the effect was much less when implementation fidelity was low.[29-30] Program adherence relates to the content and dose of the intervention. It may be moderated by the quality of training, supporting system, and participant responsiveness. More research is needed to clarify the moderating impact of the components included here in order to encourage the family to practice DIR/Floortime® at home.

Further analysis was conducted to compare gains in attention and initiation composite scores of CBRS between the parents in the invention groups who spent different amounts of time using the DIR intervention. There is no statistical difference in improvements for those children whose parents documented spending more or less time using the intervention with their children. A similar analysis was attempted to look at the effect of the different kinds of developmental disabilities across children, however, no statistical difference was detected. This finding was likely due to the small number of subjects.

Prior studies have noted a concern that parent-mediated interventions might cause increased parental stress.[31] Of additional note, we found a statistically elevated Parent-Child Dysfunctional Interaction Score of PSI. We interpret this finding in the context of both the process of training and the improvement in initiation and attention. On the one hand learning techniques for improving interactions might increase parental awareness of the problematic aspects of the relationship. Further, when a child is more able to attend to what she wants and is more able to initiate, this too may create a feeling in the parent that their relationship is harder. These concerns should be studied in more detail in future studies, particularly in light of no differences between groups in the Parental Distress Score of PSI and total PSI scores. Qualitative assessments might shed further light on the clinical impact of DIR for individual families.

Limitations

The main limitation of the current study were, first, the families in the intervention group used DIR/ Floortime® in addition to their children's routine care, whereas the control group received only their routine care. Improvements with intervention may be attributable to any amount of increase in time spent between caregivers and children.

While the effects of DIR Floortime® parent training are promising at four months, long-term effects of the intervention are unknown. Further study with more diverse caregivers, better stratification of the children regarding their challenges, and longer follow-up are needed.

Summary

Adding parent training intervention and the home-based DIR/Floortime® for 1-2 hours per day for four months produced statistically significant and clinically meaningful improvements. Further research should investigate long-term outcomes and the effects on parents' perception about their child, themselves, and their relationships with their children.

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Predictive Factors for Survival Outcomes of High-Risk Febrile Neutropenic Patients: a 3-Year Study at a Single Center in Thailand

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ABSTRACT

Objective: This study aimed to identify the risk factors associated with mortality in febrile neutropenic patients.

Materials and Methods: This 3-year, single center, retrospective, observational study was conducted at Chiangrai Prachanukroh Hospital, Chiangrai Province, Thailand. The inclusion criteria consisted of a patient age of over 15 years and a diagnosis of febrile neutropenia.

Results: Most of the 303 febrile neutropenic inpatients had a Multinational Association for Supportive Care in Cancer (MASCC) risk score < 21. The median length of stay was 6 days (interquartile range: 4-11 days). During 30 days of admission, 24.8% of the patients succumbed. In a univariate analysis, patients receiving G-CSF, the post-chemotherapy-related group, patients with MASCC score > 16, and patients admitted in private had significantly higher survival rate. In a multivariate analysis, a MASCC score ≤ 16 and non-chemotherapy-related groups were associated with an increased mortality risk.

Conclusion: The 30-day survival rate of febrile neutropenic patients in Thailand is seventy-five percent. Low MASCC score and non-chemotherapy-related neutropenia are associated with a higher risk of unfavorable outcomes.

Keywords: Febrile neutropenia; risk factors; mortality; Thailand; developing country (Siriraj Med J 2019; 71: 339-348)

INTRODUCTION

Febrile neutropenia is usually accompanied by other signs and symptoms of infection. The treatment outcomes of these patients, especially those in the high-risk group, are associated with high morbidity and mortality.[1] In cases with severe infections, previous guidelines recommend that patients should be admitted to hospital.[2,3] The hospital stays of febrile neutropenic patients with solid tumors and hematological malignancies have been reported to be approximately 1 to 2 weeks.[4] Most febrile neutropenia occurs during chemotherapy, especially in cases of hematologic malignancies and solid cancers.[5] Moreover, it could result from other neutropenia-causing diseases, for example, aplastic anemia, drug-induced agranulocytosis, HIV infections, and autoimmune diseases.[6-9] The treatment is costly due to both the length of the hospital stay and the associated complications. A retrospective study has reported the clinical and economic burden arising from the hospitalization of this patient group. The mean duration of hospitalization with febrile neutropenia in all cancer patients was 6 days and the median cost was $8,376 per episode of febrile neutropenia.[10]

These problems are present in all countries. From a previous study of patients with febrile neutropenia in a developed country, the mortality rate during admission was 10%, and the mean hospitalization duration was

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8.6 days.[11] The outcomes for developing countries still need to be documented. The present cohort study aimed to demonstrate data on the predictive factors and survival outcomes of patients with febrile neutropenia at a single center in a developing country.

MATERIALS AND METHODS

This 3-year, single center, retrospective, observational study was conducted at Chiangrai Prachanukroh Hospital, Chiangrai Province, Thailand. It focused on patients with febrile neutropenia who had been admitted to medical wards between January 1, 2014 and December 31, 2016. The inclusion criteria were (1) a patient age of over 15 years and (2) a diagnosis of febrile neutropenia. The patients were identified through the ICD-10-CM diagnosis code database using the codes for fever (R50) and agranulocytosis (D70). The primary outcome of the study was to identify the risk factors associated with mortality in febrile neutropenia. The clinical characteristics, clinical outcomes, laboratory findings, treatments and complications were recorded as secondary outcomes. This study was approved by the Ethical Committee for Research in Human Subject at Chiangrai Prachanukroh Hospital (0032.102/15693).

Terminology

Febrile neutropenia is a condition of fever > 38.3°C or > 38°C for 1 hour, with an absolute neutrophil count (ANC) of ≤ 500 cells/cu mm, or an ANC of ≤ 1,000 cells/cu mm with an expected nadir of ≤ 500 cells/cu mm.[12]

The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a scoring method for identifying low-risk of complications in cancer patients with febrile neutropenia. This score comprises the following factors: burden of febrile neutropenia, hypotension, chronic obstructive pulmonary disease, previous fungal infection, dehydration, and age. Scores ≥ 21 signify a low-risk group of complications, while scores < 21 indicate a high-risk group of complications in patients with febrile neutropenia.[13]

Multi-drug resistant (MDR) organism is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[14] Severe infection is determined as severe sepsis by clinical of systemic inflammatory response syndrome with evidence of infection and end-organ dysfunction such as altered mental status, hypotension, oliguria (urine output < 0.5 ml/kg/hr) or hypoxia.[2]

Statistical analysis

PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The sample size (330 cases) was calculated by the proportion of mortality rate between two groups from the previous study.[15] The critical value was 1.96 with 90% power. Continuous variables were represented as mean ± standard deviation, or median and interquartile range (IQR). For the continuous variables comparison consisting of age, complete blood counts and blood chemistry investigations, the results were calculated by the Mann–Whitney U test or student's t-test. Categorical variables including gender, diseases, MASCC risk index, infections and clinical outcomes were presented as frequency and percentage, and they were compared using Fisher's exact or chi-square test. The survival analysis and predictive factors associated with survival were compared using the log-rank test and presented as a Kaplan–Meier survival curve. A Cox proportional hazards analysis (enter method) was used for the univariate and multivariate factors associated with survival outcome, and they were exhibited as hazard ratio (HR) and 95% CI. A p-value < 0.05 was defined as statistically significant.

RESULTS

Baseline characteristics of febrile neutropenic patients

This study enrolled 303 cases of febrile neutropenic patients. In all, 328 cases were admitted to medical wards during the 3-year study period. Of the included cases, twenty-five were excluded: twenty-two were incompatible with the diagnostic criteria of febrile neutropenia, and the remaining three had inadequate documentation. The mean age was 53±2 years, and females predominated (51.4%). A large number of patients had hematologic diseases and solid cancers, which included acute leukemia (27.7%), solid tumors (21.1%), aplastic anemia (18.8%), and lymphoma (18.2%). The clinical severity of the patients was determined by their MASCC risk score. The median was 16 (IQR: 13-18), with 91.4% (277 cases) having a score below 21, indicating that they had a high-risk of febrile neutropenia.

According to the initial laboratory findings, the complete blood counts showed a median hemoglobin of 8.0 g/dl (IQR: 6.0–9.0 g/dl); a median ANC of 150 cells/cu mm (IQR: 13–385 cells/cu mm); a median platelet count of 28,000 cells/cu mm (IQR: 10,000-80,000 cells/cu mm). All initial laboratory results are summarized in Table 1.

Infectious etiologies, treatments, and survival outcomes

Organ-specific symptoms of infection were seen in 57.8% of patients. Respiratory tract infections were the most common (22.8%); they were followed by gastrointestinal

TABLE 1. The demographic and clinical characteristics and laboratory findings of febrile neutropenic patients.

	Febrile neutropenic patients (n = 303) Positive results (%)
Age (years), mean ± SD	53 ± 17
Gender	
Female	166 (54.8%)
Diseases	
Solid cancers	64 (21.1%)
Acute leukemia	84 (27.7%)
Aplastic anemia	57 (18.8%)
Lymphoma	55 (18.2%)
Myelodysplastic syndrome	10 (3.3%)
Multiple myeloma	3 (1.0%)
Infections	23 (9.6%)
Autoimmune disease	1 (0.3%)
Median MASCC score	16 (13–18)
0-10	63 (20.8%)
11-20	214 (70.6%)
21-23	26 (8.6%)
Laboratory findings	
Complete blood count	
Median Hb level (g/dl)	8.0 (6.0–9.0)
Median WBC count (cells/cu mm)	1,100 (600–1,800)
Median ANC count (cells/cu mm)	150 (13–385)
Median platelet count (cells/cu mm)	28,000 (10,000–80,000)
Blood chemistry	
Median creatinine (mg/dl)	1 (0.7–1.0)
Median albumin (g/dL)	3.0 (2.6–3.6)
Median total bilirubin (mg/dl)	1 (0.6–1.6)
Median direct bilirubin (mg/dl)	0.2 (0–0.7)
Median aspartate aminotransferase (U/L)	30 (20–52)
Median alanine aminotransferase (U/L)	22 (14–42)

Abbreviations: MASCC = the Multinational Association for Supportive Care in Cancer; SD = standard deviation; WBC = white blood cell; ANC = absolute neutrophil count

infections (16.8%). Nearly 20% of the patients had positive blood culture. The most common infectious organisms were gram negative bacteria: *Acinetobacter* spp. (9.2%), *Escherichia coli* (8.3%), *Pseudomonas* spp. (5.3%), and *Klebsiella* spp. (5%). Furthermore, multidrug-resistant bacterial infections were recorded at 14.5%, while fungal infections were present in a small number of patients. These results are illustrated in Table 2.

The median length of hospital stay was 6 days (IQR: 4-11 days). The median duration of an ANC below 500 cells/cu mm was 3 days (IQR: 2-7 days). Approximately 85% of cases were admitted to a common ward. Eighty-three percent of the patients received an antibiotic within 4 hours. Sixty percent of the patients had post-chemotherapy associated neutropenia, and nearly half received granulocyte colony stimulating factor (G-CSF) after developing febrile neutropenia. As to the complications, acute respiratory failure developed in 64 cases (21.1%), while another 60 (19.8%) had clinical of shock.

Of the 303 febrile neutropenic patients, 228 (75.2%) survived and were discharged from the hospital. By the 30th day of febrile neutropenia, Fifty-three patients (70% of dead cases) died during neutropenic time, before their neutrophil recovering. The common causes of death were severe infections (83.5%) and bleeding associated with thrombocytopenia (12.7%). In the mortality group, the median survival during admission was 6 days (IQR: 2–9 days), as shown in Table 2.

Risk factors associated with mortality outcome

We classified the patients into 2 groups to determine predictive factors that might impact on the survival outcomes during 30 days of admission. In a univariate analysis, a patient age ≤ 60 years had a 30-day survival rate of 77.3%, while the corresponding figure for those aged > 60 years was 69.6% (p = .175; Fig 1A). The 30-day survival rate in patients with ANC ≤ 100 cells/cu mm was not significantly different from those with ANC > 100 cells/cu mm (71.9% versus 76.2%, p = .421). The 30-day survival rate for patients receiving G-CSF was 84.9%, compared with 65.6% for those who did not receive G-CSF (p = < .001; Fig 1B). Furthermore, the post-chemotherapy-associated neutropenia group had 30-day survival rate of 83.2%, which was superior to the non-chemotherapy-related group (60.5%; p = < .001; Fig 2A). For MASCC score, the lower score is associated with higher risk of complications of febrile neutropenia. A MASCC score ≤ 16 yielded a 30-day survival rate of 58.2% whereas a MASCC score > 16 had a 30-day survival rate of 96.7% (p = < .001; Fig 2B). Patients who were admitted to a private room must be clinically stable and needed to copay for their stay. These group was found to have a 30-day survival rate of 88.4%, which was moderately higher than the 72.0% for those admitted to a general ward (p = .034; Fig 3A). In addition, patients who received antibiotics < 4 hours and ≥ 4 hours after arrived at ward had 30-day survival rate of 73.7% and 78%, respectively (p = .481; Fig 3B). Focusing on the duration of neutropenia in each group, the groups with aged > 60 years, ANC > 100 cells/cu mm, receiving G-CSF and receiving antibiotics < 4 hours had significantly shorter neutropenic duration (Table 3).

In a multivariate analysis, the results showed that an MASCC score ≤ 16 and the non-chemotherapy-related group were associated with an increased risk of mortality (HR = 16.88, 95% CI = 6.15–46.32, p = < .001; and HR = 2.37, 95% CI = 1.19-4.72, p = .014, respectively). Table 3 exhibits the univariate and multivariate analyses of the risk factors impacting on the survival outcomes of febrile neutropenic patients during 30 days of admission.

Subgroup analysis

We selected 277 patients who were categorized as a high-risk group by MASCC score to analyze the survival outcome. The patients who received G-CSF, or developed febrile neutropenia after chemotherapy, or had MASCC score > 16 were more likely to have significantly better survival outcome in a univariate analysis. In a multivariate analysis, the patients with MASCC score > 16 and those who developed febrile neutropenia after chemotherapy were correlated with better outcome (Supplementary Table S1).

Furthermore, subgroup analysis of the patients who developed febrile neutropenia after chemotherapy revealed that MASCC score ≤ 16 leaded to an increased risk of mortality when compared to those with MASCC score > 16 (HR = 58.14, 95% CI = 3.05–1,108.10, p = .007).

DISCUSSION

This study aimed to identify the risk factors associated with a fatality outcome for febrile neutropenic patients during a 30-day admission period. Approximately 70% of the patients were cancer cases. Almost all cases had a clinical severity by MASCC risk score below 21, which is considered to signify a high risk.[16] In a univariate analysis, favorable factors of survival outcome consist of chemotherapy-associated neutropenia, G-CSF exposure, admitted to private room, and MASCC score > 16. Post-chemotherapy-associated neutropenia patients had more favorable outcomes. This would be because these patients

TABLE 2. The infections, complications and outcomes of febrile neutropenic patients.

	Febrile neutropenic patients (n = 303) Positive results (%)
Infections	
Site of infection	57.8%
Respiratory	22.8%
Gastrointestinal	16.8%
Genitourinary	11.2%
Bacteremia	19.1%
Skin and soft tissue	8.9%
Head and neck	3%
Central nervous system	0.7%
Infectious organisms	37.3%
Bacteria	
Acinetobacter spp.	9.2%
Escherichia coli	8.3%
Pseudomonas spp.	5.3%
Klebsiella spp.	5.0%
Streptococcus spp.	4.6%
Staphylococcus spp.	3.3%
Enterococcus spp.	2.3%
Multidrug-resistant bacteria	14.5%
Fungus	
Penicillium spp.	2.3%
Aspergillus spp.	1.7%
Candida spp.	1.0%
Complications	
Respiratory failure	21.1%
Shock	19.8%
Median duration of ANC < 500 cells/cu mm (days)	3 (2-7)
Median length of hospital stays (days)	6 (4-11)
Outcomes on 30th day	
Death	75 (25.6%)
Median time to death (days)	6 (2-9)
Cause of death	
Infection	83.5%
Bleeding	12.7%

Abbreviation: ANC = absolute neutrophil count

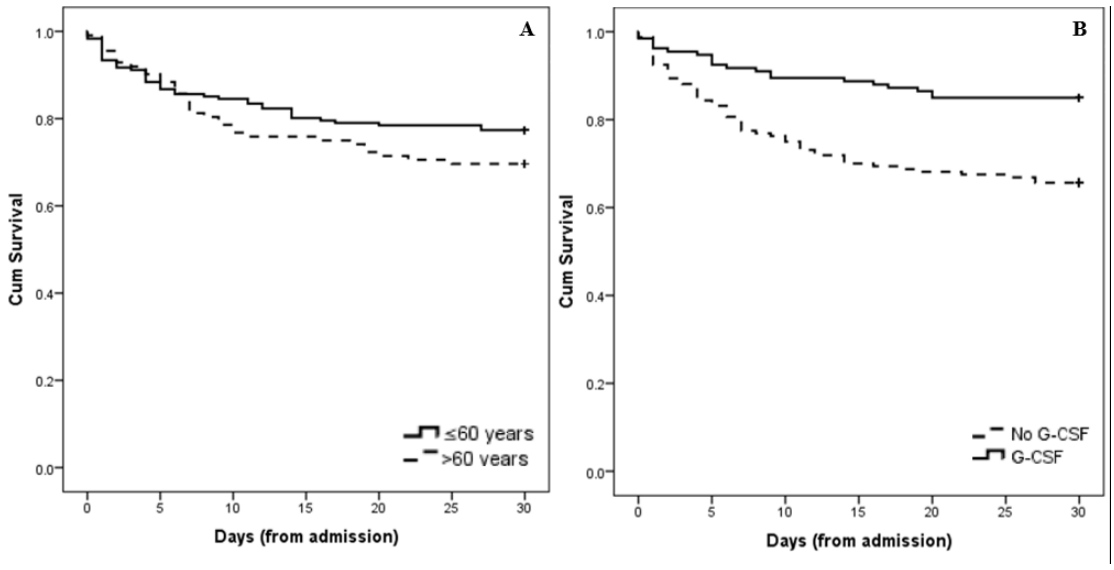


Fig 1. Overall survival curves according to (A) age groups (p-value = .175); (B) receiving G-CSF groups (p-value < .001).

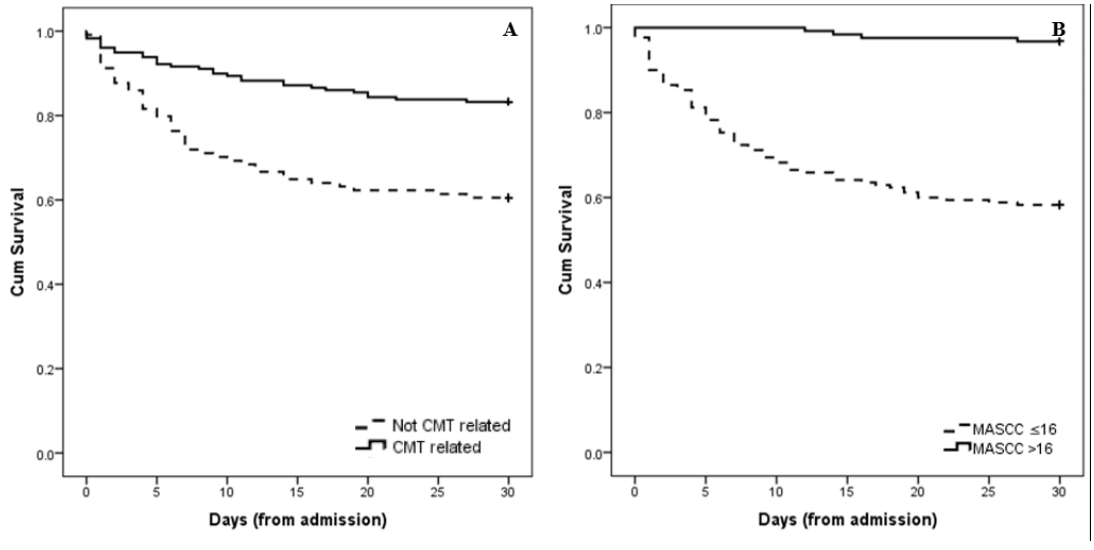


Fig 2. Overall survival curves according to (A) chemotherapy related groups (p-value <.001); (B) MASCC score groups (p-value < .001).

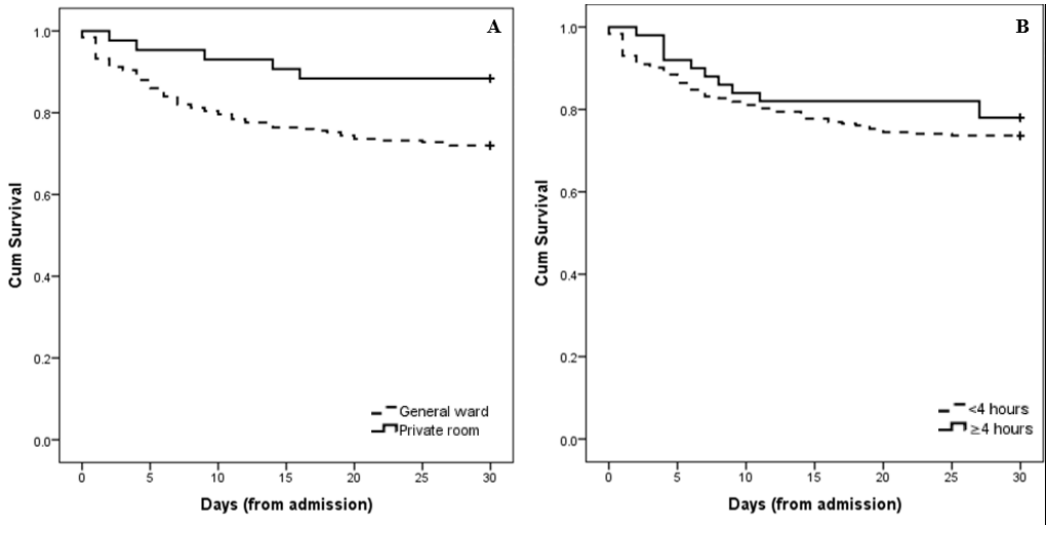


Fig 3. Overall survival curves according to (A) admitted ward-type groups (p-value = .034); (B) time to receive antibiotics (p-value =.481).

TABLE 3. Univariate and multivariate analyses for overall mortality of febrile neutropenic patients (days).

Univariate	N	Median neutropenic duration (days, IQR)	Overall survival (days)	*P*-value	HR (95% CI)
Age				.175	
≤ 60 years	181	4 (2–10)	24.8		1
> 60 years	112	2 (1–4)	23.4		1.37 (0.87–2.16)
ANC					
≤ 100 cells/cu mm	121	4 (2–8)	23.9	.421	1
> 100 cells/cu mm	172	2 (1–6)	25.4		0.83 (0.52–1.31)
G-CSF				< .001	
Yes	133	2 (2–4)	26.7		1
No	160	5 (2–11)	22.2		2.56 (1.54–4.28)
Chemotherapy				< .001	
Yes	179	2 (2–7)	26.4		1
No	114	4 (2–7)	20.9		2.74 (1.72–4.35)
MASCC score				< .001	
> 16	123	3 (2–6)	29.6		1
≤ 16	170	3 (2–9)	20.4		16.42 (5.99–44.99)
Private room				.034	
Yes	43	4 (2–10)	27.6		1
No	250	3 (2–6)	23.7		2.67 (1.08–6.61)
Time to antibiotic (hours)				.481	
< 4	243	3 (2–6)	25.6		1
≥ 4	50	6 (2–15)	24.0		1.26 (0.66–2.39)

Multivariate	*P*-value	HR (95% CI)
No G-CSF	.501	1.30 (0 .61–2.78)
No chemotherapy	.014	2.37 (1.19–4.72)
MASCC ≤ 16	< .001	16.88 (6.15–46.32)
No private room	.210	1.80 (0.72–4.49)

A *p*-value < .05 indicates statistical significance

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; G-CSF = granulocyte colony stimulating factor; HR = Hazard ratio; IQR = interquartile range, MASCC = the Multinational Association for Supportive Care in Cancer

SUPPLEMENTARY TABLE S1. Univariate and multivariate analyses for overall mortality of high-risk febrile neutropenic patients (days).

Univariate	Overall survival (days)	*P*-value	HR (95% CI)
Age		.396	
≤ 60 years	24.2		1
> 60 years	23.3		1.22 (0.77–1.94)
ANC			
≤ 100 cells/cu mm	23.1	.531	1
> 100 cells/cu mm	24.3		0.86 (0.54–1.37)
G-CSF		< .001	
Yes	26.4		1
No	21.8		2.57 (1.53–4.31)
Chemotherapy		< .001	
Yes	26.1		1
No	20.1		2.86 (1.79–4.57)
MASCC score		< .001	
> 16	29.8		1
≤ 16	20.4		43.87 (6.09–315.96)
Private room		.086	
Yes	27.7		1
No	23.2		2.42 (0.88–6.65)
Time to antibiotic (hours)		.859	
< 4	23.6		1
≥ 4	24.9		1.06 (0.55–2.05)

Multivariate	*P*-value	HR (95% CI)
No G-CSF	.438	1.36 (0 .63–2.96)
No chemotherapy	.022	2.28 (1.13–4.62)
MASCC ≤ 16	< .001	44.07 (6.09–318.79)
No private room	.716	1.21 (0.43–3.41)

A *p*-value < .05 indicates statistical significance

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; G-CSF = granulocyte colony stimulating factor; HR = Hazard ratio; MASCC = the Multinational Association for Supportive Care in Cancer

could spontaneously achieve neutrophil count recovery after their nadir period. Furthermore, a previous study has confirmed that the use of G-CSF is beneficial to short neutropenic duration in solid cancer patients with high-risk febrile neutropenia receiving chemotherapy.[17] Aplastic anemia and infection were common causes in non-chemotherapy related neutropenic group. A previous large cohort study of aplastic anemia in developing country represented the mortality rate of 9 percents.[7] In addition, increase severity of neutropenia had been reported in advanced HIV infection and leaded to fatal secondary infections.[6] G-CSF may be advantageous to temporary increase of neutrophil counts in patients with severe aplastic anemia with fever.[18] In addition, patients who admitted to private room had better outcomes because this group was possibly correlated with clinically stable, higher socioeconomic status and better nursing care. As to the factors associated with poor outcomes in the multivariate analysis, an MASCC score ≤ 16 and non-chemotherapy-related neutropenia were susceptible to a higher mortality risk. We decided to use MASCC score ≤ 16 and > 16 to divide patients into two groups because 16 is the median score of this cohort and this level was the beginning of the score that can discriminate the outcome between alive and dead. This result was correlated with a large observational study carried out by MASCC score at the beginning of febrile neutropenia in relation to bacteremia, the score <15 represented much higher mortality of 36% compared with 3% in patients with MASCC score ≥21.[19] Taking all into account, we encourage physicians to determine the MASCC score of febrile neutropenia patients early. For patients with lower MASCC scores, especially ≤ 16, or patients who have non-chemotherapy-related neutropenia, extensive investigations, intensive vital sign monitoring, and promptly antibiotics and specific treatments are needed to improve their survival outcomes.

More than 25% of the cases in this cohort died during admission, which is a higher rate than the previously reported results in a developed country.[11] We particularly focused on the survival outcomes on the 30th day of admission because the previous study had shown that the mortality rate ratios were highest within 1 month for patients treated with chemotherapy for malignant diseases.[20] Thrombocytopenic bleeding is listed as the second most common cause of death. Because there are some problems of platelet's availability and utilization of platelets depending on each physician's decision making.

The median duration of an ANC below 500 cells/cu mm was 3 days. This short duration for neutropenic recovery was probably related to the fact that 60.1% of the cases were post-chemotherapy-associated neutropenia, who typically would be able to restore neutrophils to normal levels within a few days.[21] However, many patients in this study died during neutropenic period so we cannot demonstrate the real neutrophil recovery time in this group.

The three most common sources of infection in our study were respiratory tract infections, bacteremia, and gastrointestinal tract infections. Similar to previous results, pneumonia and gastrointestinal infections were the important causes of morbidity and mortality for febrile neutropenic patients.[22] This study found that the most common infectious organisms were gram negative bacteria, with 14.5% being multidrug-resistant organisms. However, fungal infections were only present in a small number of the patients in our study. This is because of the limited availability of computerized tomography of the lungs and the long period for serum galactomannan results. These result in an under-detection of fungal infections, especially invasive pulmonary aspergillosis. The main limitation of our study is that it was a retrospective study; some data, therefore, are lacking or limited. For instance, the exact duration of febrile neutropenia could not be estimated because some patients had history of fever before admitted to the hospital. The complications of this study were mainly focused on acute respiratory failure and shock; nevertheless, other complications might be co-occurred but did not be recorded. Moreover, several primary physicians took care of the febrile neutropenic patients followed an old specific hospital protocol to prescribe antibiotics within 4 hours after making diagnosis. However, current guidelines recommend prescribing antibiotics within an hour. The indications of G-CSF for febrile neutropenia in our hospital during the study period were vary in each physicians. Fortunately, a policy for G-CSF usage in febrile neutropenia in our hospital is recently applied. Further investigation about the outcome after releasing the new policy is ongoing collected.

CONCLUSION

The 30-day survival rate of febrile neutropenic patients in Thailand is seventy-five percents. A low MASCC score and non-chemotherapy-related neutropenia are associated with a higher risk of unfavorable outcomes.

Declaration of conflicting interest: The authors have declared that no conflicts of interest exist.

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The Components of Strategic Leadership of Prosthetic and Orthotic Practitioners in Thailand

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ABSTRACT

Objectives: To determine the components and to test the validity of factor analysis of strategic leadership among prosthetic and orthotic practitioners in Thailand with the empirical data.

Methods: The sample consisted of 754 prosthetic and orthotic practitioners from 200 government hospitals in Thailand. The two instruments used were structured interview and questionnaires consisting of 66 items with Item-Objective Congruence (IOC) at 0.96 and the reliability of questionnaire in the form of Cronbach alpha coefficient was 0.98. The content analysis, exploratory factor analysis and confirmatory factor analysis were used to analyze data.

Results: There were 7 components of strategic leadership among prosthetic and orthotic practitioners in Thailand which consisted of 42 factors with factor loadings as follows: relating the part to the whole (0.997), corporate spirit (0.904), strategic thinking and planning (0.899), building partnerships (0.896), developing today' and tomorrow's leader (0.878), making it happen (0.865), and giving direction (0.823). The validity test results of factor analysis of strategic leadership among prosthetic and orthotic practitioners in Thailand were confirmed with the empirical data.

Conclusion: From the research findings, 7 components of strategic leadership should be developed among prosthetic and orthotic practitioners, particulary the first three components i.e., relating the part to the whole, corporate spirit, and strategic thinking and planning.

Keywords: Strategic leadership; prosthetic and orthotic practitioners (Siriraj Med J 2019; 71: 349-355)

INTRODUCTION

The WHO states that an estimated 0.5 percent of people with disabilities require a prosthesis or orthosis. Furthermore, in 2010, among people in Africa, Asia, and Latin America, 30 million people with disabilities required a prosthesis or orthosis and were in need of rehabilitation practitioners; Physiatrist, Certified Prosthetist and Orthotist, and Prosthetist and Orthotist Technician.[1] A Certified Prosthetist and Orthotist could treat 250 patients which means a requirement of approximately 120,000 practitioners. However there are only 34 certified institutes that can produce 600-800 practitioners annually. The production of Prosthetists and Orthotists is still a global issue which requires huge capital for machinery and adequate teaching personnel. This results in a substantial lack of Prosthetists and Orthotists practitioners in developing countries.[1] In Thailand, there are 836,224 people with disabilities in need of prosthetic and orthotic devices as of December 2016.[2] According to the WHO, a single device has a 3-year lifespan, meaning that Thailand

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requires 1,150 Prosthetists and Orthotists. Physiatrists have specific training in rehabilitation through prosthetics and orthotics. Currently there are only 381 physiatrists working in the Thai healthcare scheme,[4] and there are only 173 licensed Prosthetists and Orthotists.[5]

Nevertheless, the Sirindhorn School of Prosthetics and Orthotics, established in 2002, is an ISPO Category 1 program which has produced 100 qualified Thai Prosthetists and Orthotists until now. However, despite 100 graduates, only 71 are working in Thailand.[3] Strategic management planning is essential in order to progress human resource development. John Adair is an expert in 'Strategic Leadership' and states that leadership comprises strategic thinking and planning, giving direction, relating the part to the whole, corporate spirit, developing today's and tomorrow's leaders, building partnerships, and making it happen.[5] Strategic Leadership is a characteristic of a leader who brings about advancement to an organization and begins with a good vision and successful practices.[6] Senior management or manager is required to directly involve with every step of strategic management which consists of 3 main parts; 1) Strategic Formulation, 2) Strategic Implementation, and 3) Strategic Control & Evaluation.[7]

A review of literature did not provide any examples of research on strategic leadership among prosthetic and orthotic practitioners in Thailand and International level. There is literature on leadership in nursing[5] and some literature focuses on a model for strategic leadership development for secondary school administrators according to Durbin's theory.[7-9] This information is useful because it lays the groundwork for preliminary research on the prosthetic and orthotic profession.

This study aimed to identify the components of strategic leadership among prosthetic and orthotic practitioners in Thailand. The outcome of this research will be useful for the development of strategic leadership among prosthetic and orthotic practitioners as key succes factors of effective health service management. According to the new way of management, not only the top level is important to run the business but also middle level and frontline level. To develop strategic leadership for prosthetic and orthotic in all levels will help increase an effective health service management as a whole.

Research question

1) What are the components of the strategic leadership among prosthetic and orthotic practitioners in Thailand? and 2) Does the component structure of the strategic leadership among prosthetic and orthotic practitioners in Thailand conform with empirical data?

Objective

1) Analyze the components of strategic leadership among prosthetic and orthotic practitioners in Thailand.
2) Analyze variables of each component of strategic leadership among prosthetic and orthotic practitioners in Thailand.
3) Analyze the conformity between the components of strategic leadership among prosthetic and orthotic practitioners in Thailand with the empirical data.

Conceptual Framework

A conceptual framework, which was created based on the strategic leadership framework of John Adair (2010) was used.[10] The framework demonstrates responsibilities of the Chief Executive Officer within 7 components; Giving direction, Making it happen, Relating the part to the whole, Building partnerships, Strategic thinking and planning, Releasing corporate spirit, and Developing today's and tomorrow's leader (Fig 1).

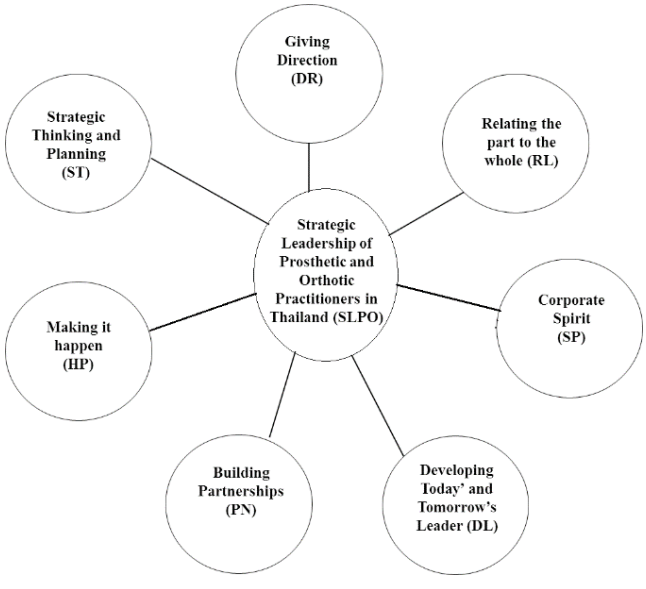


Fig 1. Conceptual framework of the components of the strategic leadership among prosthetic and orthotic practitioners in Thailand.

MATERIALS AND METHODS

From May to October 2016, questionnaires were provided to 754 prosthetics and orthotics practitioners from 200 government institutes in Thailand via post. The research was a correlational descriptive research and utilized a questionnaire of 76 questions divided into 3 parts;

Part 1: Personal Information (10 questions)

Part 2: Questionnaire of the 7 components of strategic leadership among prosthetic and orthotic practitioners in Thailand: Giving direction (7 questions), Make it

happen (7 questions), Relating the part to the whole (15 questions), Building partnerships (6 questions), Releasing corporate spirit (6 questions), Developing today's and tomorrow's leader (10 questions), and Strategic thinking and planning (14 questions)

Part 3: Comments and suggestions (1 question)

The questionnaire was adopted from "The Competencies of Strategic Leadership of Chief Nurse Executives, Private Hospital in Bangkok Metropolitan[5] which was based on Adair's concept (2010)[a]. It comprised of 7 components 76 items of strategic leadership. The researcher contacted the copyright holder and asked the permission to utilize the questionnaire which has already been translated into Thai language. At the first stage, small group discussion among 20 experts in prosthetic and orthotic, as well as human resources management was set up in order to gather comments and ideas related to the strategic leadership among prosthetic and orthotic practitioners in Thailand. The second stage, in-depth interview with 8 prosthetic and orthotic experts was arranged in order to verify the variables. Finally, the questionnaire was modified based on small group discussion and in-depth interview findings. Eleven items were deleted because they did not fit for the samples in this research study. The original questionnaire was used for the top level, but this research concerned not only the top level but the middle and the frontline level managers. Evaluated with the Index of Item-Objective Congruence (IOC), the content validity of the questionnaire was 0.96 and the reliability demonstrated in the form of Cronbach's Alpha Coefficient was 0.98.

Participants

The participants were prosthetic and orthotic executives and practitioners in government medical institutes, secondary and tertiary hospitals all over the country consisting of 200 management executives in hospitals, 381 physiatrists, 73 prosthetic and orthotic practitioners, and 100 prosthetic and orthotic technicians, so in total 754 persons participated in the study The prosthetic and orthotic executives and practitioners in private sector were not included because the administrative system between public and private medical institues was different.

Samples

The samples were physiatrists, prosthetic and orthotic practitioners, prosthetic and orthotic technicians, and hospital management executives. A questionnaire was used to first discuss 76 variables through a small group (20 persons) discussion and in-depth interview of 8 prosthetic and orthotic management executives and experts. A resulting 65 variables were used in this research because contents of variables use were for senior chief exceutive, while the prosthetic and orthotic practitioners were junior chief exceutives. As there were 754 participants, all of them were considered samples[12] and 427 questionnaires were answered on first request (56.63%). Hair et al (2010) and Comrey and Lee (1992) suggested use of factor analysis and determined that a sample should be 10-20 times of variables (650-1,300 sample of 65 variables) and 300 was sufficient for this research using AMOS program.[12-14]

Ethic approval

Ethical approval was approved by Christian University of Thailand Institutional Review Board (Protocol number 4/2015), Faculty of Medicine Siriraj Hospital, Mahidol University (Si 695/2016), Chulalongkorn University (accceptance letter no. 1955/2016) and other institutes as required.

Outcome measurement

The questionnaire was adapted from a strategic leadership capacity questionnaire provided to administrators of nursing departments at private hospitals in Bangkok and surrounding areas,[5] following concepts of John Adair.[11] The questionnaire was already translated into Thai and used in a small group discussion among 20 experts in the Prosthetics and Orthotics field in this research. Secondly, in-depth interviews with 8 prosthetic and orthotic experts were performed to verify final variables by proposive method (experts, lecturers and executive of human resource department in prosthetics and orthotics field). The questionnaire was then evaluated with the Index of Item-Objective Congruence (IOC) which scored 0.96. Thirty questionnaires were provided to prosthetic and orthotic practitioners and human resource management executives which were similar to original research samples for reliability test by Cronbach's alpha coefficient. Also, since the questionnaire was a 5-level measurement, a Cronbach's alpha coefficient was applied and resulted in a value of 0.98.

Statistical analysis

Final data analysis was performed using descriptive statistics; frequency, percentage, mean, mode, standard deviation, and inferential statistics; Exploratory Factor Analysis and Confirm Factor Analysis with AMOS version no.18.

RESULTS

Personal information of the participants verified that the proportion of male and female participants were

almost equal. Most were 31-40 years old and married (33.5%). They possessed more than 15 years of experience in prosthetic and orthotic practice (37%), had Bachelor's Degrees in Health Science (48.9%), and worked in hospitals under the Ministry of Public Health (57.6%).

Variable analysis of each component of strategic leadership among prosthetic and orthotic practitioners in Thailand provided 7 components in ranking order as Table 1. There were 7 Factor Loadings which ranged from 0.823 to 0.997; the highest was Relating the part to the whole at 0.997 while the lowest was Giving Direction at 0.823.

Result from an analysis of each component of the strategic leadership among prosthetic and orthotic practitioners in Thailand

1) Relating the part to the whole (RL) consisted of 8 variables which were (1) the leader has to clearly understand the objective of the department, (2) the leader has to clearly understand the objective of affiliated organization or unit, (3) all management executives in the department are capable of working as a team in order to create a High Performance Team, (4) the leader is able to get all members to work together to reach objectives of the organization, (5) the leader is able to get all members in the department to work together and reach objectives, (6) the leader should possess a capability to manage personal and work life for better leadership efficiency, (7) the leader should create a work life balance, and (8) creating too many changes may result in confusion and disorganization among practitioners.

2) Realizing corporate spirit (SP) consisted of 5 variables which were; (1) the leader has to be able to draw out efficiencies or strengths in practitioners upon their work, (2) practitioners expect their leader to have strategic leadership and teamwork ability, (3) the leader is required to trust in practitioners until their actions are not trustworthy, (4) the human mind is a powerful tool which can inspire practitioners to do great things, and (5) the nature of practitioners are normally good as a human beings.

3) Strategic thinking and planning (ST) consisted of 7 variables which were; (1) the leader ought to regularly listen to the prosthetic and orthotic management team regarding their strategic and innovative thinking, (2) the leader's strategic planning of the department should be flexible and up-to-date, (3) the leader ought to regularly listen to the hospital executive or management team upon their strategic and innovative thinking, (4) the leader should improve the strategic management of the department in order to provide services at ease, (5) the leader should encourage providing rewards for creative innovation, (6) the leader should create opportunity for practitioners to take part in developing innovation within the department, and (7) creative innovation can encourage achievement in terms of personnel, team, and device productions.

4) Building partnerships (PN) consisted of 5 variables which were; (1) other than income from service provisions, practitioners are required to be aware of benefits for the community, (2) the leader should take part in assisting the department and should get along well with domestic

TABLE 1. Variables analysis of each component of strategic leadership among prosthetic and orthotic practitioners in Thailand.

No	Components	Factor loadings
1.	Relating the part to the whole (RL)	.997
2.	Releasing Corporate Spirit (SP)	.904
3.	Strategic Thinking and Planning (ST)	.899
4.	Building Partnerships (PN)	.896
5.	Developing Today' and Tomorrow's Leader (DV)	.878
6.	Making it happen (HP)	.865
7.	Giving Direction (DR)	.823

alliances outside the hospital, (3) the device service provision, employment policy, and environmental impacts are corporate social responsibilities of prosthetic and orthotic department, (4) the leader should take part in assisting the department to get along well with international alliances of different cultures, and (5) the department will be more successful if the leader expands to have more alliances in terms of device service provision.

5) Developing today' and tomorrow's leader (DV) consisted of 7 variables which were; when a practitioner is appointed to be a management executive, the leader will also have to (1) evaluate the team management of each executive, (2) evaluate the management competency of the assigned works, (3) evaluate the leadership regularly, (4) evaluate the characteristic of a leader, (5) the leader should initiate a career development system for practitioners to be at a management executive level in the future, (6) the leader should make the management executives believe that they are able to train leadership to practitioners, and (7) the leader should launch a policy for the management executives to be responsible for self-development.

6) Making it happen (HP) consisted of 5 variables which were; the leader has to administrate all segments in the department to focus on the customers (1) by initiating quality control system of prosthetic and orthotic service provision, (2) by initiating a quality control system of service provision, (3) by initiating a security system of service provision, (4) the leader should take part in rectifying the problem in case the management executives under the department failed to achieve their goals, and (5) the leader should always follow up progression and review the strategic planning of the department.

7) Giving direction (DR) consisted of 5 variables which were; (1) the leader has to create a mutual vision in order to make the department a future organization, (2) the leader can clearly explain the core value of the responsible department, (3) practitioners have to clearly understand their roles which conform to the direction of organization, and their own responsibility, (4) the leader can clearly explain the core values which indicate the direction of the organization, and (5) the leader has to clearly understand the main objectives of the department or the organization, and know what to do in the moment and in the future.

Result from the analysis of the congruence of the component of the strategic leadership among prosthetic and orthotic practitioners in Thailand with the empirical data

After adjusting the relationship model through a Confirmatory Factor Analysis, the CMIN/Df = 1.590, Root Mean Squared Residual (RMR) = 0.18, Root Mean Squared Error of Approximate Residual (RAMSEA) = .037, Tucker Lewis Index (TLI) = .968, and Comparative Fit Index (CFI)=.975, were found to conform to the empirical data by consistent tolerance index. Therefore, the model was consistent with the empirical data on the components as illustrated in Table 2 and Fig 2.

TABLE 2. Model of a Confirmatory Factor Analysis of the component of the strategic leadership among prosthetic and orthotic practitioners in Thailand with the empirical data.

Consistency Index	Tolerance Index	Adjusted Model	
		Statistical Index	Consistency
χ(FD/NIMC) fd/^{2}	Less than 3	1.590	Consistent
Root Mean Squared Residual (RMR)	Not more than 0.8	.018	Consistent
Goodness of Fit Index (GFI)	More than 0.9	.900	Consistent
Adjust Goodness of Fit Index (AGFI)	More than 0.9	.863	Consistent
Root Mean Square Effort of Appr.(RMSEA)	Less than 0.08	.037	Consistent
Tucker Lewis Index (TLI)	More than 0.9	.968	Consistent
Comparative Fit Index (CFI)	More than 0.9	.975	Consistent

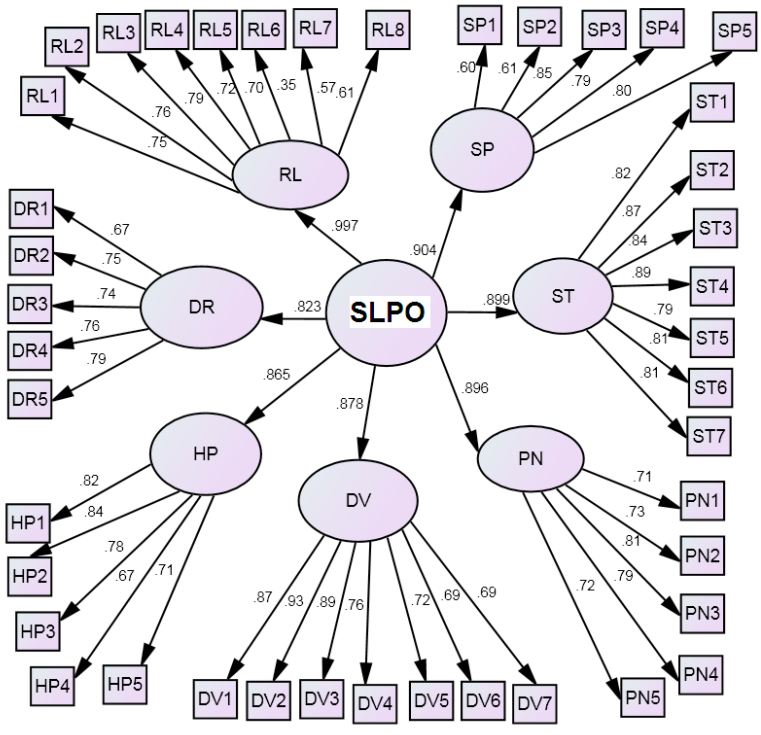


Fig 2. Structural pattern of the component of the strategic leadership among prosthetic and orthotic practitioners in Thailand

DISCUSSION

The difference between the survey of prosthetic and orthotic practitioners in Thailand and the Confirmatory Factor Analysis (CFA) of the component of the strategic leadership among prosthetic and orthotic practitioners in Thailand

The survey outcome on the components of strategic leadership among practitioners in Thailand demonstrated giving precedence to the component consecutively as follows; giving direction ($\overline{X}$= 4.56, SD = 0.58), make it happen ($\overline{X}$ = 4.53, SD = 0.59), strategic thinking and planning ($\overline{X}$ = 4.46, SD = 0.62), relating the part to the whole ($\overline{X}$ = 4.43, SD = 0.63), develop today's and tomorrow's leader ($\overline{X}$ = 4.32, SD = 0.67), building partnerships ($\overline{X}$ = 4.31, SD = 0.68), and releasing corporate spirit ($\overline{X}$ = 4.14, SD = 0.74). On the other hand, the outcome of CFA turned out to fall in an alternative order of precedence; relating the part to the whole (factor loading = 0.997), releasing corporate spirit (factor loading = 0.904), strategic thinking and planning (factor loading = 0.899), building partnerships (factor loading = 0.896), develop today's and tomorrow's leader (factor loading = 0.878), make it happen (factor loading = 0.865), and giving direction (factor loading = 0.823).

Such different outcomes of precedence levels from the research were due to the fact that practitioners considered the components of strategic leadership separately and gave precedence to external environment which evidences an increase of people with disabilities that augments the demand of practitioners and treatment.[1] Still, the CFA helped to determine whether the variable was a reasonable and systematic construct in the theoretical model or not.[12] According to the CFA, each variable has an effect on each other and concerns a possible deviation on the overall model.

The Confirmatory Factor Analysis of the component of the strategic leadership among prosthetic and orthotic practitioners in Thailand demonstrated that all 7 components were consistent with the empirical data.

The research outcome reaffirmed the component of strategic leadership of John Adair (2010) responsibility for Chief Executive Officer. All 7 components conformed with the research outcome of strategic leadership capability of the chief executive of the nursing department at hospitals in Bangkok and surrounding areas.[5]

This research outcome reaffirmed that a strategic leader is required to predict future directions of the organization and initiate strategic planning to pursue the objectives.[6] This research outcome demonstrated that the most significant components relate the part to the whole, releasing corporate spirit, and strategic thinking and planning. Whereas the research outcome observed in nursing management demonstrated that the most significant components were strategic thinking and planning, relating the part to the whole, and developing

today's and tomorrow's leader.[5] This similarity is as a result of practitioners being medical personnel who provide assessment, design, invent, and produce prostheses and orthoses for people with disabilities,[13] while nurses provide hospitalized care to people, families, and communities by instructing, suggesting, consulting, giving health counsel, physical and mental contact, environmental care, rehabilitating, provision of primary care, and assisting the specialist in treating diseases.[14] By doing so, both careers are connected by a medical profession which shares a similar responsibility to take care of people with disabilities.

The component of strategic leadership among prosthetic and orthotic practitioners in terms of relating the part to the whole is a first priority.

Regarding to a process of providing medical care, prosthetics and orthotic devices to the patient requires communication, coorperation, and assistance from various practitioners; prosthetic and orthotic practitioners, technicians, orthopaedists, physiatrists, surgeon, physiologists, nurses, mechanical engineers, and rehabilitation staff. Relating the part to the whole, thus, is the most important component for the strategic leader to understand about the objectives and working system of their department and organization. Also, individuals will have to work as a team to in order to create a chief executive team that is highly efficient.

Recommendations to apply the research outcome in the organization administration

1.1 This research discovered that relating the part to the whole is the most significant component, and therefore the organization must pay close attention in order to enhance the strategic leadership of practitioners, especially in their understanding of objectives of the organization. Being consistent with the objectives of the affiliated organization and team work is compulsory, and will lead to an effective chief executive and team leader.

1.2 The providing direction is the least significant component, but the most agreed component by practitioners. Therefore, the organization should support and improve by creating shared vision in order to move forward to a future organization, and increase a clear core value picture in responsibility of departments. Moreover, a clear understanding of the role, direction of organization, and personal responsibilities is also essential.

Recommendation for future research

1. Creating guidelines for strategic leadership of practitioners in Thailand and facilitating progress by initiating training centered on strategic leadership development programs.

2. Future research should consider related components of strategic leadership with operational performance of practitioners.

3. Creating research of strategic leadership in other medical fields such as Physiotherapists, and Thai Traditional Medicne, etcetera.

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Correlation between Heart Failure with N-Terminal-Pro-B Type Natriuretic Peptide and Cardiothoracic Ratio from Chest Radiograph in Pediatric Heart Disease

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ABSTRACT

Objective: The aim of this study is to determine the correlation between the symptom of heart failure and basic investigations; N-Terminal-Pro-B Type Natriuretic Peptide (NT-proBNP) and cardiothoracic (CT) ratio from chest radiograph in pediatric heart disease.
Methods: One-hundred-eighty children (aged 1-15 years) with underlying heart disease were enrolled in this prospective cross-sectional study. The heart failures were categorized based on the Ross classification into 2 groups, non-heart failure (Ross classification I) and heart failure (Ross classification II-IV). The NT-proBNP level was determined and chest radiograph was done in posteroanterior upright position for CT ratio.
Results: The mean NT-proBNP level was 223.1 pg/ml (±180.3) and a mean CT ratio was 53.6% (±5.6) in the non-heart failure group. The mean NT-proBNP level was 1,054 pg/ml (±1,840.3) and a mean CT ratio was 58.6% (±6.1) in heart failure group. There was a significantly positive correlation between heart failure symptoms and the level of NT-proBNP and CT ratio. In this study, the cut-off value of NT-proBNP for heart failure was more than 400 pg/ml (OR 6.97, ROC 0.694, sensitivity 52.6%, specificity 86.3%) and CT ratio more than 55% (OR 3.57, ROC 0.654, sensitivity 68%, specificity 62.8%).
Conclusion: In pediatric heart diseases, there are strong positive correlations between heart failure with both NT-proBNP and CT ratio. These correlations help in the diagnosis of heart failure. NT-proBNP level more than 400 pg/ml and CT ratio more than 55% are indicative of heart failure in our population. Both investigations are inexpensive, readily available and do not require specialist experts.

Keywords: NT-proBNP; cardiothoracic ratio; heart failure (Siriraj Med J 2019; 71: 356-363)

INTRODUCTION

Pediatric heart diseases are more often than not congenital and less frequently acquired disease. Heart failure is one of the most important problems in pediatric cardiology clinic. The etiologies of heart failure from congenital heart diseases are mainly from volume over load and/or pressure over load. A normally-structured heart in which the disease left ventricle function in opposite to its normal function is most common cause of heart failure.[1] The clinical signs of heart failure in children include poor feeding, respiratory distress, poor weight gain, edema and exercise intolerance. There are

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standard guidelines for diagnosis and treatment of heart failure for adult in worldwide practice.[2-4] In children, the practice guidelines reviewed by many studies showed no uniformed recommendation for diagnosis and treatment of heart failure due to variant pathophysiology in pediatric heart failure and small studies subjects.[5-7] These studies suggested that we should combine symptoms, physical examinations, investigations for diagnosis and treatment and reliant on the pathophysiology of heart failures in individual children.

In out-patient department, the investigations which most readily available in every hospital and useful for diagnosis of heart failures in children are chest radiography, electrocardiogram, blood test for neuro-hormonal activation; brain natriuretic peptide (BNP) and N-Terminal-Pro-B Type Natriuretic Peptide (NT-proBNP). NT-proBNP and cardiothoracic ratio from chest radiograph are widely used with a standard cut-off value for heart failure in adult, but there is no consensus for children. Contributing factors are the various types of ventricular impairment, underlying cardiac morphology, age, gender, and assay method for NT-proBNP affecting the reference values for both markers. For chest radiograph one usually calculates the CT ratio for determination of cardiomegaly in the diagnosis of heart failure. The aim of this study was to determine the correlation between symptoms and signs of heart failure with basic investigations; NT-proBNP and CT ratio from chest radiograph in pediatric heart diseases.

MATERIALS AND METHODS

We performed a prospective cross-sectional study on 180 children (aged 1-15 years) with underlying heart diseases with diagnosis and follow-ups at the cardiology clinic of Department of Pediatric, Faculty of Medicine, Naresuan University, Thailand from September 2015 to May 2018. The study was approved by the Ethics Committee of Naresuan University (COA No. 208/2015). Heart failure was categorized by a pediatric cardiologist based on Ross classification[8] during follow up in cardiology clinic. The patients were categorized into 2 groups: non-heart failure (Ross classification I) and heart failure (Ross classification II-IV). The baseline characteristics: age, gender, underlying heart diseases, current medication and body mass index (BMI) were recorded.

The NT-ProBNP level was assayed with 3 ml of heparinized blood and immunoassay by Roche cobas h 232 instruments (Roche Diagnostics Ltd. CH-6343, Rotkreuz, Switzerland). The normal adult range of this assay is 0-300 pg/ml, and a value of more than 450 pg/ml is suggestive of heart failure in adult with age below 50 years.[3,4] Presently, there are no clear standards and there is no consensus of normal range for children.

The chest radiograph was done in posteroanterior upright position for CT ratio. Patients who could not have chest radiographs done in upright position were excluded from the study. The CT ratio is the ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter (inner edge of ribs) in chest radiography.

Prior to performing the procedures, all patients and their parents (or families) were briefed on the risks and benefits of the procedure. Only upon consent from the patients and their families were the procedure carried out.

Sample size

The proportion of NT–pro-BNP in patients with heart failure in Evelyn Lechner et al showed the NT–pro-BNP in patients with heart failure to be 0.39 and patients without heart failure was 0.6; 2, Alpha of 0.05; 3 and Beta of 0.2 for testing two independent proportions (two-tailed test).[9] The total sample size of 176 patients.

Statistical analysis

Continuous data with normal distribution were shown as mean and standard deviation (SD) and those with non-normal distribution as median and minimum: maximum. Categorical data was shown as frequency and percentage. The odds ratio and 95% confidence interval (95%CI) were used to compare the association between NT–pro-BNP and CT ratio presence of heart failure. A receiver operating characteristic (ROC) analysis was used to determine the diagnostic utility of NT-proBNP and CT ratio for heart failure. A p-value of less than 0.05 was regarded statistically significant.

RESULTS

The study consisted of 180 patients, 91 males (50.6%) and 89 females (49.4%) patients. In all the subjects, the mean age was 6.3 years (±4.3 years), the mean weight was 21.7 kg (±12 kg), the mean height was 112.9 cm (±26.7 cm) and the mean BMI was 15.6 (±2.9). The diagnosis of heart disease was categorized into 3 major hemodynamics groups; ventricular volume load (62.2%), ventricular pressure load (22.2%) and combine ventricular load (15.6%). The diagnosis in ventricular volume load group was (1) left to right shunt lesion: ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA) (2) valvular regurgitation: mitral valve regurgitation (MR), aortic valve regurgitation (AR), Ebstein's anomaly with tricuspid valve regurgitation

(TR), rheumatic heart disease with valvular regurgitation (3) postoperative total correction of tetralogy of Fallot (TOF) with pulmonary valve regurgitation (PR). The diagnosis in ventricular pressure load group was (1) valvular stenosis: pulmonary valve stenosis (PS), aortic valve stenosis (AS), corrected translocation of great artery (TGA) with severe PS, VSD with severe PS (2) TOF with moderate to severe PS (3) pulmonary hypertension (PHT) or Eisenmenger's complex: complete atrioventricular canal defect (CAVD) with PHT, Double Outlet Right Ventricle (DORV) with PHT (4) coarctation of aorta (COA). The diagnosis in combine ventricular load group was single ventricle (SV) with postoperative Glenn's operation, SV with postoperative aortopulmonary shunt or pulmonary artery banding, pulmonary atresia (PA) with VSD postoperative aortopulmonary shunt. For all patients, the mean NT-proBNP was 583.1 pg/ml (±1,282.9) with median of 225 pg/ml (19:9,000) and a mean of CT ratio was 55.7% (±6.3) with median of 56% (40.3:84) (Table 1). The Fig 1 and 2 are the distribution of NT-proBNP level and CT ratio of all patients in each Ross classification group.

TABLE 1. Clinical characteristics, NT-proBNP and CT ratio of patients in heart failure and non-heart failure group.

Characteristic	All patients (n=180)		heart failure (n=78)		Non-heart failure (n=102)		P-value
	n	%	n	%	n	%	
Sex (male)	91	50.6	35	44.9	56	54.9	0.182
Age (year)							0.199
1-5	94	52.2	45	57.7	49	48.0	
6-15	86	47.8	33	42.3	53	52.0	
Mean (±S.D.)	6.3	(±4.3)	5.9	(±4.5)	6.6	(±4.1)	
Weight (kg)							0.074
Mean (±S.D.)	21.7	(±12)	19.9	(±12)	23.1	(±11.8)	
Height (cm)							0.006
Mean (±S.D.)	112.9	(±26.7)	106.7	(±27.8)	117.7	(±24.9)	
BMI (kg/m^2)							0.963
Mean (±S.D.)	15.6	(±2.9)	15.6	(±3.3)	15.6	(±2.6)	
Diagnosis							<0.001
Ventricular volume load	112	62.2	33	42.3	79	77.5	
Ventricular pressure load	40	22.2	17	21.8	23	22.5	
Combine ventricular load	28	15.6	28	35.9	0	0.0	
NT-proBNP (pg/ml)							
Mean (±S.D.)	583.1	(±1282.9)	1054	(±1840.3)	223.1	(±180.3)	
Median (min : max)	225	(19 : 9000)	406.5	(19 : 9000)	171	(44 : 1080)	
CT ratio							
Mean (±S.D.)	55.7	(±6.3)	58.6	(±6.1)	53.6	(±5.6)	
Median (min : max)	56	(40.3 : 84)	57.9	(40.3 : 84)	53.9	(42.3 : 68.8)	

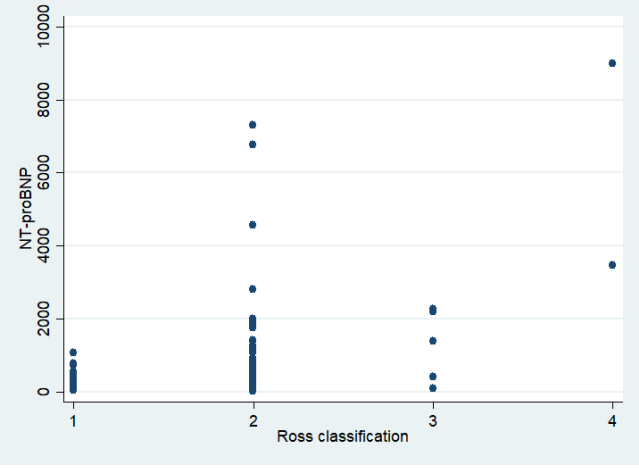


Fig 1. Scatter plot of NT-proBNP level grouped by Ross classification in all patients.

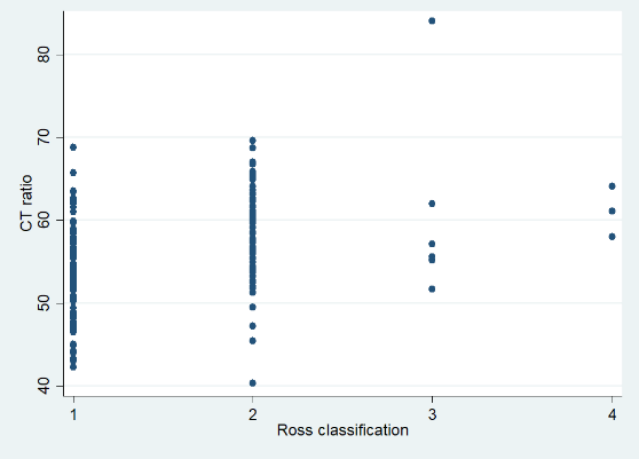


Fig 2. Scatter plot of CT ratio grouped by Ross classification in all patients.

Non-heart failure group

The non-heart failure group (n=102, 56.7%), defined as asymptomatic patients with Ross classification class I, included 56 males (54.9%) and 46 females (45.1%). The mean age was 6.6 years (±4.1 years), the mean weight was 23.1 kg (±11.8 kg), the mean height was 117.7 cm (±24.9 cm) and the mean BMI was15.6 (±2.6). The diagnosis in this group revealed that the patients had mainly acyanotic heart disease (99%) which consisted of 77.5% of ventricular volume load 22.5% of ventricular pressure load and no diagnosis of combine ventricular load. The mean NT-proBNP was 223.1 pg/ml (±180.3) with median of 171 pg/ml (44:1080) and a mean of CT ratio was 53.6% (±5.6) with median of 53.9% (43.3:68.8) (Table 1).

Heart failure group

The heart failure group (n=78, 43.3%), defined as symptomatic patients with Ross classification class II-IV, included 35 males (44.9%) and 43 females (55.1%). The majority of Ross classification in this group was class II (88%) The mean age was 5.9 years (±4.5 years), the mean weight was 19.9 kg (±12 kg), the mean height was 106.7 cm (±27.8 cm) and the mean BMI was 15.6 (±3.3). The diagnosis in this group was acyanotic heart disease in 49%, which consisted of 42.3% of ventricular volume load, 21.8% of ventricular pressure load and 35.9% of combine ventricular load. The mean NT-proBNP was 1,054 pg/ml (±1,840.3) with median of 406.5 pg/ml (19:9,000) and a mean CT ratio was 58.6% (±6.1) with median of 57.9% (40.3:84) (Table 1). There were significant differences between heart failure and non-heart failure group in both NT-proBNP level and CT ratio (p<0.05) (Figs 3-4).

The NT-proBNP level base on hemodynamic groups

The mean NT-proBNP in ventricular volume load group was 920.9 pg/ml (±1,772.7) in the heart failure group and 213.6 pg/ml (±182) in the non-heart failure



Fig 3. The box-plot of NT-proBNP level in patients with clinical heart failure and non-heart failure.



Fig 4. The box-plot of CT ratio in patients with clinical heart failure and non-heart failure.

group. The mean of NT-proBNP in ventricular pressure load group was 1381 pg/ml (±2656.3) in heart failure group and 255.6 pg/ml (±174.3) in non-heart failure group. The mean NT-proBNP in combine ventricular load group was 1012.3 pg/ml (±1,289.3) in heart failure group (Table 2).

Correlation between Heart failure and NT-proBNP

The correlation of NT-proBNP between the 2 subgroups of symptom (non-heart failure and heart failure group) showed a significant positive correlation with area under the curve (AUC) of receiver operative characteristic (ROC) curve of 0.697 (Fig 5). The level of NT-proBNP showed an increase correlation with a higher level indicating greater possibilities for heart failure. The cut-off value of NT-proBNP from our study for diagnosis of heart failure in pediatric heart disease population was more than 400 pg/ml with sensitivity at 52.6%, specificity at 86.3% (Table 3).

Correlation between Heart failure and CT ratio

The correlation of CT ratio with 2 subgroups of symptom (non-heart failure and heart failure group) showed a significant positive correlation with AUC of ROC curve 0.728 (Fig 5). The CT ratio showed increase correlation when higher level of CT ratio indicated higher odd for heart failure. The appropriate cut-off value from our study for diagnosis heart failure in pediatric heart disease was a CT ratio more than 55% with sensitivity at 68%, specificity at 62.8% (Table 4).

DISCUSSION

The brain natriuretic peptide (BNP) and NT-proBNP are synthesized by ventricular myocytes in response to the pressure load, the volume load or an increase in myocardial wall stress. Both hormones are the most well studied biomarker for diagnosis of heart failure in adult and children. In this study, we found a significant and strong positive correlation between NT-proBNP

TABLE 2. The NT-proBNP level in hemodynamic subgroup.

Diagnosis	All patients (n=180) NT-proBNP (pg/ml)		Heart failure (n=78) NT-proBNP (pg/ml)		Non-heart failure (n=102) NT-proBNP (pg/ml)	
	Mean	(±S.D.)	Mean	(±S.D.)	Mean	(±S.D.)
Ventricular volume load	422	1016.9	920.9	1772.7	213.6	182
Ventricular pressure load	733.9	1797	1381	2656.3	255.6	174.3
Combine ventricular load	1012.3	1289.3	1012.3	1289.3	NA*	NA*

*no patient in this subgroup

TABLE 3. The correlation of clinical of patients with NT-proBNP.

Outcome	NT-proBNP (pg/ml)		
	>300	>350	>400
Odds ratio (95% CI)	4.43 (2.34 to 8.38)	6.14 (3.09 to 12.20)	6.97 (3.40 to 14.28)
ROC	0.672	0.692	0.694
Sensitivity (%)	59.0	55.1	52.6
Specificity (%)	75.5	83.3	86.3

TABLE 4. The correlation of clinical of patients with CT ratio.

Outcome	CT ratio (%)		
	>50	>55	>60
Odds ratio (95% CI)	8.46 (2.84 to 25.14)	3.57 (1.92 to 6.65)	4.87 (2.18 to 10.86)
ROC	0.631	0.654	0.624
Sensitivity (%)	94.9	68.0	34.6
Specificity (%)	31.4	62.8	90.2

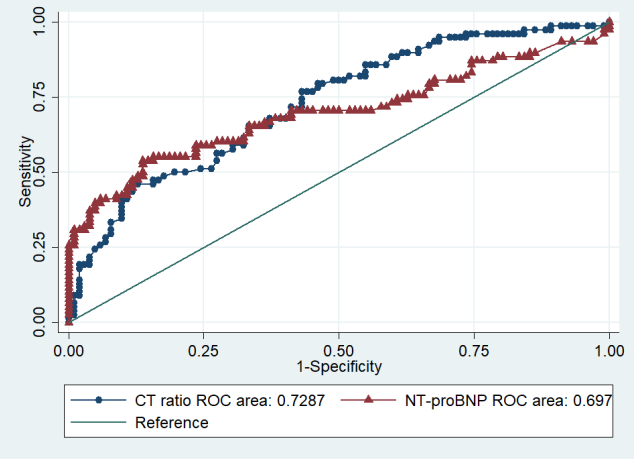


Fig 5. The ROC curves of NT-proBNP and CT ratio for the diagnosis of heart failure in pediatric heart disease population.

and CT ratio with clinical of heart failure in children with underlying heart disease. These results are similar to the previous studies showing a correlation between NT-proBNP and symptoms and signs of pediatric heart failure defined with New York Heart Association (NYHA), Ross and modified Ross classification scores.[9-11]

In non-heart failure group, the mean NT-proBNP level (mean 223.1±180.3 pg/ml, median 171 pg/ml) in this study was almost within the normal range in healthy children, when matched with age and sex in A CALIPER pilot study. The reference value of immunoassay for NT-proBNP level using the same kit as ours from A CALIPER pilot study showed the level in boys and girls age 1 to 5 years to be 12.5-308.4 pg/ml and those aged 5 to 15 years to be 7.9-177.9 pg/ml.[12] Another study by A Nir, et al which studied the reference value of NT-proBNP using a similar method in 58 normal children (4 months to 15 years) showed normal 5-391 pg/ml, median 90 pg/ml.[13] In this study, in hemodynamic asymptomatic children, there was no different in the mean of NT-proBNP as compare to the previous normal reference value. This result suggested that even with underlying heart disease, the NT-proBNP would exhibit similar level. These children had minimal ventricular load and wall stress. Our result was different from A Uner and colleagues study on NT-proBNP level in symptomatic, asymptomatic heart disease and control normal children. It showed significant different level of NT-proBNP among the 3 groups.[14] This observation may be due to the larger sample size of pediatric heart disease in ours study.

Similar to the previous studies, in heart failure group, the mean NT-proBNP was significantly higher than asymptomatic patient. The previous studies showed higher NT-proBNP level in children with heart failure compared to normal children.[10,13-14] F-J Zhou, et al found that the children with congenital heart disease admitted to hospital with pneumonia and heart failure had higher NT-proBNP level than those with pneumonia alone.[15] We also observed that ventricular wall stress might be higher in the pressure load group than volume load or combined ventricular load based on NT-proBNP level (Table 2). The combined ventricular load group consisted mainly of patients with cyanotic complex congenital heart disease with all subjects having symptomatic heart failure with elevation of NT-proBNP values and higher than symptomatic ventricular volume load group. The systematic review in usefulness of brain natriuretic peptide in complex congenital heart disease by Jannet A Eindhoven, et al showed result to be the same as our study.[16] Evelyn Lechner, et al were studied in single ventricle heart disease and the results showed that the RV morphology yielded a higher NT-proBNP than the LV morphology. It is thus concluded that the morphologic right ventricle might be more stressed as a systemic ventricle than the morphologic left ventricle.[9]

The cut-off value of NT-proBNP for diagnosis of heart failure in children was not well established. The NT-proBNP cut off value in acute heart failure for adult aged below 50 years yielded a figure of more than 450 pg/ml with sensitivity at 98% and specificity at 76% form PRIDE study.[17] In children, a previous study by Masaya Sugimoto, et al showed cut-off value in symptomatic heart failure for patients with heart disease aged below 3 years of more than 438 pg/ml with sensitivity at 88.7%, specificity at 91.8%. In patient aged more than 3 years, it was more than 295.2 pg/ml with sensitivity at 94.7%, specificity at 95.9%.[18] The other study by Murat Sahin showed that the cut-off value for diagnosis ventricular dysfunction in children between 4 months to 17 years old was more than 514 pg/ml with sensitivity at 95%, specificity at 80%.[11] In our study done with the same analysis of NT-proBNP showed a nearly cut off value as Masaya Sugimoto study in which NT-proBNP of more than 400 pg/ml had sensitivity at 52.6% and specificity at 86.3% for diagnosis of heart failure in children aged more than 1 year old.

The other commonly used investigation for diagnosis heart failure is chest radiograph. Although echocardiogram, cardiac catheterization, cardiac MRI and multi-detector CT are now commonly used imaging techniques to investigate cardiac disease, the chest radiograph is still necessary for first step of investigation. To evaluate of cardiac enlargement, the CT ratio from chest radiograph has long been accepted as the method of choice.[19] The accepted upper limit of normal CT ratio is 50% in children and adult and 60% in infant.[20] The diagnostic accuracy from CT ratio for evaluation of function both LV and RV from many studies showed low accuracy.[21-22] In LV systolic function showed no significant association with CT ratio in patients with preserved left ventricular ejection fraction who had undergone computed tomography coronary angiography. But the CT ratio correlated with LV size and LV ejection fraction (LVEF) in patients with depressed LVEF.[21] In another study, The CT ratio reflected atrial dilatation rather than ventricular dilatation.[22] Our study showed a significant positive correlation of CT ratio with symptomatic heart failure in pediatric heart disease. The appropriate cut-off value of CT ratio was more than 55% (OR 3.57; 1.92-6.65, ROC 0.654, sensitivity at 68%, specificity at 62.8%) for the diagnosis of heart failure in pediatric heart disease. This result was similar to the study of Konstantinos Dimopoulos, et al, in which cardiomegaly was present in both simple and complex adult with congenital heart disease and CT ratio more than 55% corrected with the patients' symptom and predicted an 8-fold increased risk of death.[23]

CONCLUSION

The NT-proBNP level and CT ratio are helped in the diagnosis of heart failure in pediatric heart disease. NT-proBNP level more than 400 pg/ml and CT ratio more than 55% were predictive of heart failure in our population. Both investigations are inexpensive, readily available and do not require specialist experts for interpretation.

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Ocular Manifestations in Acute Herpes Zoster Ophthalmicus

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ABSTRACT

Objective: To determine the prevalence and clinical predictors of ocular involvement in acute herpes zoster ophthalmicus.
Methods: A retrospective chart review of 167 patients presenting with acute herpes zoster ophthalmicus at the Outpatient Department of Ophthalmology, Siriraj Hospital, was performed. All skin lesions along the ophthalmic branch of the trigeminal nerve (CN V_1) and ocular inflammatory signs were observed and documented.
Results: A total of 160 cases were analyzed. The prevalence of ocular inflammation in acute herpes zoster ophthalmicus was 73.1% (117/160). The types of ocular inflammations included conjunctival injection (99.1%), keratitis (51.3%), and iridocyclitis (21.4%). Nasociliary skin lesions (Hutchinson's sign) were the best predictor of ocular inflammation in acute herpes zoster ophthalmicus (p = 0.006, OR = 3.6, 95% CI: 1.5-9.1). Other factors associated with ocular inflammation were a period of longer than 4 days from the onset of rash to an eye examination (p = 0.007, OR = 3.2, 95% CI: 1.4-7.5), and the initiation of systemic acyclovir treatment after 3 days from rash onset (p = 0.037, OR = 2.3, 95% CI: 1.05-4.96).
Conclusion: There is a high prevalence of ocular inflammation in acute herpes zoster ophthalmicus, especially among individuals with Hutchinson's sign and delayed systemic acyclovir treatment. General practitioners should be aware of ocular involvement and refer high-risk patients for a complete ophthalmologic assessment.

Keywords: Herpes zoster ophthalmicus; Hutchinson's sign; acyclovir; ocular inflammation; uveitis (Siriraj Med J 2019; 71: 364-369)

INTRODUCTION

Herpes zoster ophthalmicus (HZO) is a reactivation of the varicella-zoster virus (VZV), a DNA-virus in the Herpesviridae family, along the ophthalmic division of the trigeminal nerve (CN V_1) after a previous infection such as chickenpox.[1-2] The clinical course usually starts with prodromal symptoms like fever, malaise, headache, and dysesthesia for approximately 1-4 days prior to the development of skin lesions. The skin manifestations are characterized by maculopapular rashes and vesicles along the CN V_1 dermatome, including the forehead, eyelids, and nose. The vesicles can progress to pustules and occasionally hemorrhagic vesicles, with the formation of crusts in 7-10 days.

The nasociliary nerve, a branch of the ophthalmic nerve, supplies both the nasociliary dermatome and intraocular tissue. The nasociliary dermatome extends from the tip and sides of the nose to the nasal bridge and medial canthus. The involvement of the nasociliary nerve presents as a variety of vesicular eruptions at the periorbital area, which can lead to a wide range of ocular inflammations (for instance, conjunctivitis, episcleritis, scleritis, keratitis, uveitis, optic neuritis, and oculomotor palsy). The subsequent ocular complications consist of

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chronic uveitis, neuralgia, and neurotrophic keratopathy.[1,3,7-8] The intraocular involvement of HZO, especially uveitis and optic neuritis, can lead to multimorbidity, including blindness, if HZO is not recognized early or treatment is delayed.

The involvement of this dermatome (Hutchinson's sign) is considered a highly sensitive sign for ocular involvement in patients with HZO.[3-4] The immune status of the patients is another factor that can dictate the likelihood and types of ocular presentation of HZO.[5-7] To the best of our knowledge, there has been no study of the prevalence and risk factors of ocular involvement in acute HZO in Thailand. Therefore, this study collected the clinical data of Thai patients with acute HZO to determine the prevalence of ocular involvement in HZO and the predictors associated with ocular inflammation.

MATERIALS AND METHODS

The study was approved by the Siriraj Institutional Review Board (Si 179/2009). A retrospective chart review of patients who were clinically diagnosed with HZO and attended the Outpatient Department of Ophthalmology, Siriraj Hospital, between 2005 and 2008 was performed. All patients underwent an eye examination under a slit-lamp biomicroscope within 1 month of the onset of skin lesions. The degree of conjunctival injection was referenced from the Cornea and Contact Lens Research Unit grading scale (none, mild, moderate, and severe).[9] However, the clinical grading of the intraocular inflammations was modified from the cell grading system of the Standardization of Uveitis Nomenclature (SUN) Working Group by using a 1 mm x 1 mm slit beam under a slit-lamp examination (grade 0 = none; grades 0.5–1+ = mild; grade 2+ = moderate; and grades 3–4+ = severe).[10] Excluded were patients with previous ocular diseases, ocular trauma, or ocular surgery, or patients who had an eye examination later than 1 month after the onset of their skin lesions.

The diagnoses of HZO were based on the presence of a unilateral group of vesicles on an erythematous base and a painful skin rash within the ophthalmic dermatome. The following data were collected and recorded: demographic data (age, sex, and race), pre-existing diseases (acquired immune deficiency syndrome, diabetes mellitus, tuberculosis, autoimmune diseases, lymphoma, pregnancy, and others), and the date of onset of the skin rash. The extent of herpes zoster skin lesions was documented by marking anatomical drawings at the eyelids, forehead, alar, and tip of the nose.

The patients were treated with systemic oral acyclovir as soon as the diagnosis of HZO was established, and the time interval between the onset of HZO and the administration of the oral antiviral drug was recorded. Oral acyclovir (800 mg, 5 times per day) was prescribed for a period of 7–10 days, as per the guidelines of the American Academy of Family Physicians.[5]

The quantitative data were analyzed using the unpaired t-test method. The qualitative data were analyzed with the Chi-square and Fisher's exact tests. Multivariate analysis was performed with a backward stepwise logistic regression method. The odds ratio (OR) with 95% confidence interval (95% CI) and p-values were calculated. Two-sided p-values ≤ 0.05 were considered statistically significant.

RESULTS

Having been diagnosed with HZO, 167 patients were referred to the Ophthalmology Department to undergo an eye examination. Of those, seven were excluded (two due to an incomplete examination, one with a history of ocular surgery, and four with incomplete records). Data on the remaining 160 patients were summarized and analyzed.

Table 1 shows the demographic data of the 160 patients, who comprised 103 females (64.4%) and 57 males (35.6%) with a mean age of 51.5 ± 18.8 years (range 5-88). The median age of our subjects was also 51 years (interquartile range 39.0-65.7). There were no differences between including or excluding patients with extreme ages. The HIV patients tended to be younger than the non-HIV patients (mean age 46.37 ± 17.63 years versus 40.32 ± 7.25 years, respectively). The study revealed 22 patients (33.8%) who were anti-HIV positive from the 65 patients who underwent an anti-HIV test; 23 patients (14.4%) with hypertension; 11 patients (6.9%) with diabetes mellitus; 8 patients (5.0%) with tuberculosis; 8 patients (5.0%) with immunodeficiency; 4 patients (2.5%) with lymphoma; and 3 patients (1.9%) with systemic lupus erythematosus. The skin lesions were confined to the forehead in 134 patients (83.8%), the eyelids in 138 patients (86.3%), and the tip of the nose (or Hutchinson's sign) in 54 patients (33.8%). The median time from the appearance of the rash to acyclovir treatment was 3 days (range 1-30 days), and from the rash appearance to eye examination was 4 days (range 1-30 days).

Ocular involvement was found in 117 patients (73.1%) with a female predilection (74 females and 43 males), but there was no difference in laterality. Almost all patients (116/117) had a conjunctival injection with mild severity (70.1%). About half of the HZO patients with ocular involvement demonstrated corneal lesions that were dendritic, stromal keratitis, or both. Iridocyclitis

TABLE 1. Demographic data of all 160 patients with acute herpes zoster ophthalmicus.

Characteristics	N (Total = 160)
Age (years)	51.5 ± 18.8
Gender: Female	103 (64.4%)
Male	57 (35.6%)
Underlying diseases	
Acquired immunodeficiency syndrome	22/65 (33.8%)
Hypertension	23 (14.4%)
Diabetes mellitus	11 (6.9%)
Tuberculosis	8 (5.0%)
Other immunodeficiency	8 (5.0%)
Lymphoma	4 (2.5%)
Systemic lupus erythematosus	3 (1.9%)
Skin involvements	
Forehead	134 (83.8%)
Eyelids	138 (86.3%)
Tip or alar of nose (Hutchinson's sign)	54 (33.8%)
Median duration (days)	
Rash to acyclovir treatment (min, max)	3 (1, 30)
Rash to eye examination (min, max)	4 (1, 30)

was the only intraocular involvement seen in this cohort, accounting for 21.4% (25/117; Table 2).

A univariate analysis demonstrated that the prevalence of ocular involvement increased significantly if a patient presented with Hutchinson's sign (p = 0.008, OR = 3.5, 95% CI: 1.4-8.4) or an HIV infection (p = 0.024, OR = 9.1, 95% CI: 1.1-7.5); if the period from the onset of rash to an eye examination was > 4 days (p = 0.009, OR = 3.1, 95% CI: 1.4-7.1); or if the period from the rash onset to acyclovir treatment was > 3 days (p = 0.044, OR = 2.3, 95% CI: 1.08-4.9; Table 3). There was no statistical significance for the age of onset, sex, or other pre-existing diseases.

As to the multivariate analysis, HIV infection showed no statistically significant association with ocular involvement. In contrast, the 3 remaining factors (Hutchinson's sign, a period from rash onset to eye examination > 4 days, and a period from rash onset to acyclovir treatment > 3 days) significantly increased the risk of ocular complications (Table 4).

A subgroup analysis for different types of ocular involvement revealed associations between Hutchinson's sign and conjunctivitis (OR = 3.6, 95% CI: 1.48-8.76), keratitis (OR = 1.97, 95% CI: 1.0-3.85), and anterior

TABLE 2. Ocular findings in acute herpes zoster ophthalmicus patients.

Characteristics	N = 117
Laterality	
Right eye	67 (57.3%)
Left eye	50 (42.7%)
Conjunctival injection	
No	1 (0.9%)
Yes	116(99.1%)
Mild	82 (70.1%)
Moderate	32 (27.3%)
Severe	2 (1.7%)
Keratitis	
No	57 (48.7%)
Yes	60 (51.3%)
Dendrite	47 (40.2%)
Stromal	7 (6.0%)
Combined	6 (5.1%)
Iridocyclitis	
No	92 (78.6%)
Yes	25 (21.4%)
Mild	14 (12.0%)
Moderate	7 (6.0%)
Severe	4 (3.4%)

uveitis (OR = 2.74, 95% CI: 1.13-6.62). After adjusting for three factors (HIV status; a period from rash onset to eye examination > 4 days; and a period from rash onset to acyclovir treatment > 3 days), there were changes in the associations between Hutchinson's sign and conjunctivitis (OR = 4.17, 95% CI: 1.58-10.97), keratitis (OR = 2.18, 95% CI: 1.07-4.42), and uveitis (OR = 3.23, 95% CI: 1.28-8.18).

TABLE 3. Univariate analysis of factors associated with ocular involvement in acute herpes zoster ophthalmicus.

Factors	Ocular involvement (N = 117)	No ocular involvement (N = 43)	Odds ratio (95% confidence interval)	P-value#
Age (years)	50.4 ± 18.6	54.5 ± 19.4	–	0.227
Gender: Female	74 (63.2%)	29 (67.4%)	1.3 (0.5–3.1)	0.76
Duration of rash to eye examination >4 days	53 (45.3%)	9 (20.9%)	3.1 (1.4–7.1)	0.009*
Duration of rash to acyclovir treatment >3 days	60/114 (52.6%)	13/40 (32.5%)	2.3 (1.08–4.9)	0.044*
Underlying diseases				
HIV infection**	21/51 (41.2%)	1/14 (7.1%)	9.1 (1.1–75)	0.024*
Hypertension	15 (12.8%)	8 (18.6%)	0.6 (0.2–1.6)	0.503
Diabetes	9 (7.7%)	2 (4.7%)	1.7 (0.4–8.2)	0.729
Tuberculosis	7 (6.0%)	1 (2.3%)	2.7 (0.3–22.4)	0.683
Immunodeficiency	5 (4.3%)	3 (7.0%)	0.6 (0.1–2.6)	0.444
Lymphoma	4 (3.4%)	–	–	0.575
Systemic lupus erythematosus	3 (2.6%)	–	–	0.564
Skin involvement				
Forehead	99 (84.6%)	35 (81.4%)	1.3 (0.5–3.1)	0.804
Eyelid	103 (88.0%)	35 (81.4%)	1.7 (0.7–4.3)	0.411
Tip or alar of nose (Hutchinson's sign)	47 (40.2%)	7 (16.3%)	3.5 (1.4–8.4)	0.008*

#Unpaired t-test for quantitative data and Chi-square test, Fisher's exact test for qualitative data
*Statistical significance at p-value < 0.05, **Human immunodeficiency virus infection

TABLE 4. Multivariate analysis of factors associated with ocular involvement in acute herpes zoster ophthalmicus.

Factors	Crude odds ratio (95% confidence interval)	P-value#	Adjusted odds ratio (95% confidence interval)	P-value##
Hutchinson's sign	3.5 (1.4-8.4)	0.008*	3.6 (1.5-9.1)	0.006*
Duration of rash to acyclovir treatment >3 days	2.3 (1.08-4.9)	0.044*	2.3 (1.05-4.96)	0.037*
Duration of rash to eye examination >4 days	3.1 (1.4-7.1)	0.009*	3.2 (1.4-7.5)	0.007*
HIV infection**	9.1 (1.1-75)	0.024*	6.3 (0.8-49.9)	0.084

#Univariate analysis by Chi-square test
##Multivariate analysis by backward stepwise logistic regression
*Statistical significance at p-value < 0.05
**Human immunodeficiency virus infection

DISCUSSION

HZO is a common disease, and it may present not only as a skin manifestation but also involve ocular tissue. The ocular manifestations of HZO are variable; the acute eruptive phase can present as eyelid swelling, conjunctivitis, punctate keratitis, and/or corneal pseudodendrites. After the acute eruptive phase, the infection can cause stromal keratitis, nummular keratitis, disciform keratitis, neurotrophic keratopathy, and corneal mucous plaque. Severe ocular involvement has been reported as serpiginous keratitis, acute retinal necrosis, optic neuritis, orbital myositis, and cranial nerve palsy, but especially CN III and orbital apex syndrome, resulting in retinal detachment or a loss of vision. The clinical findings in the chronic phase include persistent corneal epithelial defects and postherpetic neuralgia.[8,11-13]

In the current report, we studied the ocular involvement of acute HZO. The age of onset of HZO for our cohort was about 50 years. This was younger than the ages found by Canadian and European studies, in which HZO was reported to occur at an age of approximately 60,[3,4,14] but it was much older than the age reported from Africa (around 35 years).[15-16] This may suggest that the age of HZO onset may have racial and/or geographic variations. Furthermore, we also found females were more predominant than males. In terms of the underlying diseases, previous studies by Nassaji-Zavareh et al. and Kaiserman et al. demonstrated a significant correlation between herpes zoster infection and diabetes mellitus, but not specific to HZO.[17-18] In our study, the proportion of diabetes mellitus patients was only 6.9% (11 patients), which is low. Therefore, we could not analyze the association between diabetes mellitus and herpes zoster infection.

We found that the most common skin lesions in HZO occurred on the eyelids, followed by the forehead and, least commonly, the tip of the nose. It is known that the virus replicates and migrates peripherally along the sensory nerve; when it reaches the skin, it can penetrate the epidermis and subsequently develop into skin lesions.[8] From previous studies, the most frequent nerve which the VZV affects is the frontal branch of the trigeminal nerve, which innervates the upper eyelid and forehead.[7,19-20] This explains why our study found those areas were the most common sites of HZO involvement.

The rate of ocular involvement in acute HZO in our study was 73.1%, which is comparable to the 74% involvement reported by Adam et al.[14] On the other hand, the rate is slightly higher than that found by Zaal et al. (63%).[19] However, the rate of ocular involvement in the HZO patients in the study by Zaal et al. was lower than in the present study because Zaal et al. only included immunocompetent patients, and they were also referred to ophthalmologists earlier than in our study. The vast majority of ocular involvement in the current study was in the form of conjunctivitis (99.1%), which tended to subside gradually only after systemic oral antiviral treatment; some of the patients needed further attention. In addition, half of the patients (51.3%) with eye complications demonstrated keratitis (dendritic, stromal, or a combination), which needed topical antiviral therapy. About one-fifth of the patients (21.4%) had an intraocular involvement (iridocyclitis). As to other studies, Szwto et al. also found that conjunctivitis was the most common ocular manifestation.[21]

Our univariate analysis established a significant correlation between HIV infection and ocular involvement in HZO, but not for diabetes mellitus. Nevertheless, HIV infection did not have a significant association with ocular involvement in HZO after adjustment by the multivariate analysis. This mainly resulted from the low number of patients in the study who had undergone HIV testing. In contrast, a larger number of HIV patients was demonstrated by van Dyk et al. to have a strong association between HIV and ocular involvement.[22] It is recognized that a positive HIV status can lead to serious complications due to an individual's immunodeficiency. Therefore, even though HIV status was not significantly associated with ocular complications in our study, we suggest that all HIV patients with HZO should be examined by ophthalmologists to detect ocular complications and prevent the development of the most devastating forms.

The higher risk of ocular manifestations in HZO had a statistically significant association with Hutchinson's sign, a period > 4 days from rash onset to eye examination, and a period > 3 days from rash onset to acyclovir treatment. Hutchinson's sign (or skin involvement of the alar and tip of nose) demonstrated a statistically significant association with ocular involvement, whereas other skin involvement did not. In the study by Adam et al., ocular involvement in HZO and rash along the supratrochlear nerve distribution had a statistically significant correlation.[14] VZV is reactivated from the ophthalmic division of the CN V; the ophthalmic division gives rise to the terminal branches, namely, the supraorbital, supratrochlear, and nasociliary branches. The nasociliary branch innervates the skin of the tip of the nose and divides into the long ciliary nerve, which provides sensory innervation to the cornea and uvea.[8] This therefore explains why the common ocular complications in HZO patients are keratitis and uveitis. A previous study by Harding et al. also found that uveitis was the common manifestation in HZO (46.48%).[3] From this evidence, a rash appearing

along the nasociliary branch (Hutchinson's sign) or the supratrochlear branch could suggest that the HZO patients concerned have a high risk of ocular complications.

Treatment with an oral antiviral drug can arrest viral replication in the early phase of HZO, thereby stopping the progression and dissemination of the virus. We found there was a significant association between ocular involvement and both a duration of > 4 days from the onset of skin rash to the time of eye examination, and a duration of > 3 days from the onset of skin rash to systemic acyclovir administration. These data therefore indicate that a delayed examination or treatment allows the virus to migrate to the distant ophthalmic nerve, thereby increasing the risk of ocular involvement.

Given the low number of subjects, the current study did not find any severe ocular findings. Other studies have reported devastating forms of ocular manifestations, such as orbital myositis, ophthalmoplegia, optic neuritis, cranial nerve palsy, and orbital apex syndrome.[11-12] Nonetheless, we should take special care with HZO patients who have decreased visual acuities. This state could indicate that the patient has a chance of developing serious ocular complications.

The limitations of this study were related to its use of a retrospective chart review, which provided limited data, especially for underlying diseases such as HIV. An HIV test was performed in only 65 patients (40.6%), not all patients, and there were no records of viral loads or CD4 counts available to stage the severity of the HIV disease. Another limitation of our study was the subjective evaluation of the ocular inflammation grading (both for conjunctival and uveal involvements), which varied between the graders. However, this should not affect the main study results of the binary evaluation of ocular involvements.

CONCLUSION

HZO has been reported to cause many ocular complications. It is reactivated by an impaired host immune defense against VZV. There is a high prevalence of ocular inflammation in acute HZO, especially among individuals with positive Hutchinson's sign, delayed eye examination, and/or delayed acyclovir treatment. The data suggests that general practitioners should circumspectly assess HZO patients because any delay in diagnosis and treatment can result in severe ocular complications and increased morbidity. Patients who are suspected of having an ocular involvement should be referred to an ophthalmologist with haste.

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Association Between Body Mass Index and Moderate-to-Severe Vasomotor Symptoms in Thai Postmenopausal Women

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ABSTRACT

Objective: Body mass index (BMI) has been controversially reported to be positively, inversely, or not associated with vasomotor symptoms (VMS) in postmenopausal women. This study analysed the association between BMI and moderate-to-severe VMS in Thai population.

Methods: A cross-sectional study was conducted among 178 Thai postmenopausal women aged 30-60 years. They were categorized into two groups by BMI. The two groups (normal BMI <25.0 kg/m^2 and high BMI ≥25.0 kg/m^2) were compared. Modified menopausal rating scale (MRS) was used to assess the severity of VMS. The association between BMI, types and duration of menopause, and VMS were analyzed by chi-square test and *t*-test analysis. Multiple logistic regression analysis was used to evaluate the associations between BMI, other variables, and severity of VMS.

Results: Each group comprised 89 consecutive postmenopausal women. The percentage of women with moderate-to-severe VMS was significantly higher in the normal BMI group than in the high BMI group (60.9% vs 39.1%, respectively; p= 0.007). The association between normal BMI and moderate-to-severe VMS was statistically significant after adjustment for other confounding variables that included age, medical illness, duration or type of menopause and current medications (adjusted odd ratios [OR]: 2.378; 95% confidence interval [CI]: 1.273, 4.447).

Conclusion: Interestingly, Thai postmenopausal women with a normal BMI experience a higher rate of moderate-to-severe VMS than those with a high BMI. The finding indicates that BMI is a risk factor for VMS among Thai postmenopausal women. Healthcare providers should focus on normal BMI Thai postmenopausal women when assessing for and treating VMS.

Keywords: BMI; VMS; postmenopausal women; Thai (Siriraj Med J 2019; 71: 370-376)

INTRODUCTION

Menopause is recognized after 12 months' absence of menstruation. The typical age range for onset of menopause is 47 to 50 years.[1] Menopausal symptoms such as vasomotor symptoms (VMS: hot flushes and night sweats), sleeplessness, urinary frequency, vaginal dryness, anxiety and depression, adversely affect quality of life.[2,3] In general, VMS persists for six months to two years, but they may last for more than 10 years.[4-6] The frequency and severity of VMS are different in each

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woman. The prevalence of VMS varies widely across populations and ethnicities. Approximately 40-70% of postmenopausal women experience VMS.[7]

VMS affects quality of life by causing insomnia, depression, anxiety and fatigue. There are many methods for treating VMS such as lifestyle modifications, taking vitamin supplements, and/or using herbs.[4,6-8] Hormonal therapies (e.g., estrogen and tibolone) and non-hormonal therapies (e.g., clonidine, gabapentin, and some serotonin and serotonin–norepinephrine reuptake inhibitors), are also used for treating VMS. However, the easiest and most widely available treatment method is change in lifestyle. Women with moderate-to-severe VMS are indicated for hormonal therapy.[9]

The pathophysiology of VMS is not well understood. The first hypothesis is that a central event that is initiated in the hypothalamus drives an increase in core body temperature, metabolic rate and skin temperature. Another hypothesis is that estrogen withdrawal or deficiency causes VMS. This hypothesis is supported by the effectiveness of estrogen therapy for relieving VMS.[9] The physical and financial burdens of VMS are considerable. If practitioners know the risk factors for VMS, they can advise postmenopausal women regarding the behaviors to avoid or adopt in order to relieve the symptoms of VMS, and reduce the probability of developing VMS. Lower BMI was reported to be a risk factor for VMS.[10,11] The large SWAN cross-sectional study found BMI to be positively correlated with self-reported hot flashes and/or night sweats.[12] One recent study reported that obese women have a more symptomatic menopausal transition compared to normal weight women.[13] However, some previous studies did not find association between BMI and VMS among postmenopausal women.[14-16]

If we could identify postmenopausal women at high risk for VMS, we could develop appropriate preventive strategies including lifestyle modifications and surveillance in postmenopausal women. Accordingly, the aim of this study was to investigate the association between BMI (normal *vs.* overweight) and moderate-to-severe VMS in Thai postmenopausal women.

MATERIALS AND METHODS

This retrospective cross-sectional study, was conducted during 2012-2013 among consecutive new menopausal patients who attended the Gynecologic Endocrinology Unit, of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 2008-2011. The protocol for this study was approved by the Ethic Committee of Faculty of Medicine Siriraj Hospital (Si 659/2011).

The target population included naturally, surgically and prematurely menopausal women aged 30–60 years. Women currently using of hormonal therapies or drugs that affect VMS (e.g., SSRIs, clonidine, and gabapentin) were excluded. Detailed menopausal symptoms were obtained from subject response to structured questions (modified menopausal rating scale, modified MRS). The scale was originally developed and validated over several years by a research network consisting of many institutions located in Germany during the 1990s. [Thai questionnaire Version 5.0 (validation with permission), was used for the research "Menopause-related symptoms and quality of life in peri- and postmenopausal women in Thailand: multicenter study" that was published in Asian Biomedicine 2017;11:207-15]. The objectives of MRS were to measure the severity of menopausal symptoms, changes before and after treatment with hormone replacement therapy, and their impact on health-related quality of life. The patients first read a menopausal symptoms list, including VMS. They then ranked the level of severity from 0-4 (no symptom, mild, moderate and severe symptoms, respectively). Scores of 0 and 1 were classified as mild symptoms, and scores of 2, 3, or 4 were classified as moderate-to-severe symptoms.[17,18]

The sample size was calculated based on a pilot study of 20 patients who were divided into two groups: normal weight (BMI <25kg/m^2) and overweight (BMI ≥25kg/m^2) according to World Health Organization's definitions.[19] BMI was calculated as weight in kilograms (kg) divided by height in meter squared (m^2). The results revealed that 4 of 10 patents in the normal weight group experienced moderate-to-severe VMS. In the overweight group, only 2 of 10 patients experienced moderate-to-severe VMS. The estimated sample size (type I error of 5 %, and type II error of 20%) was 81 patients in each group. The estimated sample size was increased by 10% to compensate for missing or incomplete data. Patients were consecutively recruited from 2008 until the total sample size of 89 participants per group was achieved, as shown in Fig 1.

Retrieved demographic and clinical data included age, body weight, height, medical history, health behaviors, such as smoking and alcohol use, type of menopause, current medication, hormone replacement therapy, and severity of menopausal symptoms.

Statistical analysis

The study variables were compared among groups using the SPSS 18.0 statistical package. Chi-square test and Fisher's exact test were used for categorical data. T-test

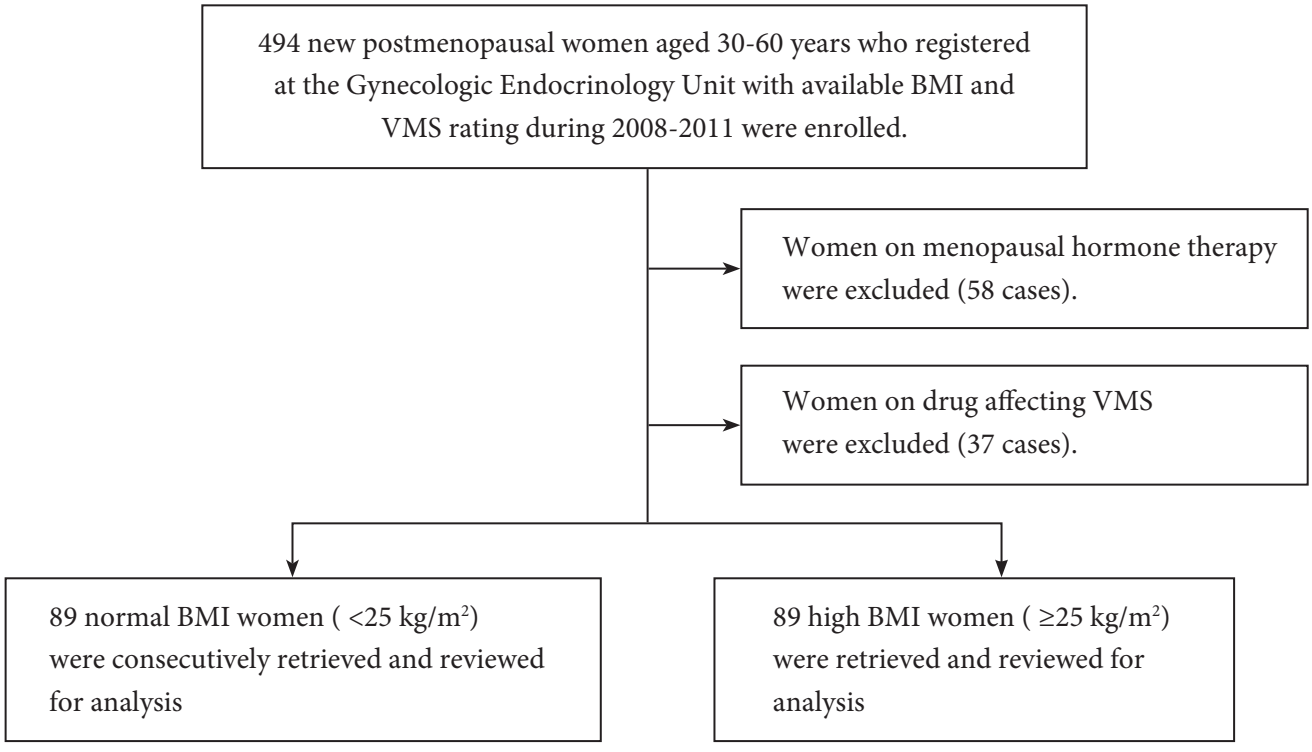


Fig 1. Flow diagram of the subject selection process.

was used for analyzing continuous data. Multiple logistic regression analysis was used to estimate the association between each of the independent variables, and for adjusting for potential confounders. The adjustments were used for independent variables, including BMI, age, medical illness, duration of menopause, type of menopause, and current medication. Significant level was defined as p-value <0.05.

RESULTS

One hundred and seventy-eight postmenopausal women that were included in this study. Characteristics of the normal weight and overweight groups are presented in Table 1. In addition, both groups of participants were non-smoking and non-alcohol drinking. The demographic and clinical characteristics were similar between groups except for age, medical illness, and antihypertensive drug use. The mean duration of menopause was not significantly different between groups. Aside from hypertensive drug use, there were no differences between groups for current medications.

The associations between BMI and severity of VMS, type of menopause, duration of menopause and other variables are shown in Table 2. Postmenopausal women with BMI <25 kg/m² were significantly more likely to report moderate-to-severe VMS than higher BMI postmenopausal women (p =0.004). No significant association was observed between severity of VMS and type or duration of menopause, age, medical illness, or current medication.

After adjustment for covariates using multiple logistic regression, the normal weight group was significantly associated with greater odds of reporting moderate to severe VMS as shown in Table 3. Only the association between normal BMI and moderate to severe VMS remained significant after adjustment for age, medical illness, duration of menopause, type of menopause and current medication (adjusted odd ratios [OR]: 2.378; 95% confidence interval [CI]: 1.273, 4.447).

DISCUSSION

One of the most commonly studied menopausal symptoms associated with obesity is VMS. Obesity was reported to be a protective factor for VMS.[20,21] On the contrary, the finding from this study in Thai population showed a different result. Thai postmenopausal women with a BMI <25 kg/m² were more likely to experience moderate - to - severe VMS than women with a higher BMI after adjusting for confounding variables.

The result of this study may be explained by estrone, which is a predominant form of estrogen in postmenopausal women that is produced in adipose tissue via the conversion of androstenedione. We assumed that women with lower BMI might have less adipose

TABLE 1. Characteristics of study population.

	BMI <25 kg/m² (N=89)	BMI ≥25 kg/m² (N=89)	P-value
Age (Mean±SD, yr)	51.87 ± 5.35	53.47 ± 4.22	0.028
Type of menopause (case, %)			0.332
Natural menopause	60 (67.4%)	56 (62.9%)	
Surgical menopause	29 (32.6%)	31 (34.8%)	
Premature menopause	0 (0%)	2 (2.2%)	
Duration of menopause (Mean±SD, yr)	4.84 ± 4.63	5.34 ± 4.53	0.467
Medical illness (case, %)	24 (26.7%)	36(40.9%)	0.044
Hypertension	12 (13.3%)	23 (26.1%)	0.032
Diabetes mellitus	4 (4.4%)	7 (8%)	0.331
Dyslipidemia	10 (11.1%)	13 (14.8%)	0.467
Chronic kidney disease	1 (1.1%)	0 (0%)	1
Thyroid disease	3 (3.3%)	2 (2.3%)	1
Allergy	1 (1.1%)	1 (1.1%)	1
Gout	2 (2.2%)	0 (0%)	0.497
CA breast	2 (2.2%)	0 (0%)	0.497
Cerebrovascular disease	1 (1.1%)	0 (0%)	1
Osteoporosis	2 (2.2%)	1 (1.1%)	1
Current medications (case, %)	19 (21.1%)	27 (30.7%)	0.145
Antihypertensive drug	9 (10%)	20 (27%)	0.022
Anti-hyperglycemic drugs	3 (3.3%)	5 (5.7%)	0.494
Hypolipidaemic agents	7 (7.8%)	11 (12.5%)	0.296
Thyroid drug	2 (2.2%)	0 (0%)	0.497
Allopurinol	2 (2.2%)	0 (0%)	0.497
Tamoxifen	2 (2.2%)	0 (0%)	0.497
Bisphosphonate	1 (1.1%)	1 (1.1%)	1

tissue, so they might have lower estrone and a higher risk of developing VMS. A lower level of estrogen is also one of the possible causes of VMS. There are many reports that support the results of this study. A group of postmenopausal women was divided into two subgroups and estrogen levels were measured and compared. The results showed that the severe VMS group had lower levels of estrone, estradiol, and body weight than the other group that never experienced VMS (p <0.05).[22] The result of our study supported one former study of naturally postmenopausal women that found that overweight women suffered from hot flushes and perspiration less than thinner women.[10] Another later study also found the risk of VMS to be higher in heavier women. A cross-sectional study of women aged 40-60 years that were classified according to BMI (≤24.9, 25.0–29.9, or ≥30 kg/m²)

TABLE 2. The association between BMI, type of menopause, duration of menopause, age, medical illness, current medications and severity of VMS.

	Vasomotor symptoms		
	Mild (N=91)	Moderate - to - severe (N=87)	P-value
BMI			0.004
< 25 kg/m^2	36 (39.6%)	53 (60.9%)	
≥ 25 kg/m^2	55 (60.4%)	34 (39.1%)	
Type of menopause			0.372
Natural menopause	58 (63.7%)	58 (66.7%)	
Surgical menopause	31 (34.1%)	29 (33.3%)	
Premature menopause	2 (2.2%)	0 (0%)	
Duration of menopause (Mean±SD, yr)	5.42 ± 4.47	4.74 ± 4.69	0.326
Age (Mean±SD, yr)	52.75 ± 4.63	52.59 ± 5.35	0.829
Medical illness	33 (35.9%)	27 (31.4%)	0.528
Current medications	25 (27.2%)	21 (24.4%)	0.675

TABLE 3. Multivariable logistic regression model for moderate to severe VMS.

	Unadjusted odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	P-value
BMI			
< 25 kg/m^2	2.38 (1.307-4.359)	2.38 (1.273-4.447)	0.007
≥ 25 kg/m^2	1	1	
Type of menopause			
Natural menopause	1.033	0.868	0.7
Surgical menopause	1	1	
Premature menopause	NA	NA	
Age	0.996 (0.938-1.058)	1.024 (0.954-1.099)	0.512
Duration of menopause	0.97 (0.909-1.035)	0.973 (0.901-1.052)	0.496
Medical illness	0.818 (0.439-1.526)	0.938 (0.333-2.64)	0.904
Current medications	0.86 (0.442-10697)	1.033 (0.344-3.1)	0.953

Abbreviations: CI = Confidence Interval, NA = not applicable

investigated the relationship between lifestyle factors (e.g., BMI and smoking) and moderate-to-severe VMS. The result showed that BMI ≥30 kg/m^2 was associated with an increased risk of moderate-to-severe hot flashes when compared with BMI ≤24.9 kg/m^2 (adjusted OR: 2.1, 95% CI: 1.5-3.0) in premenopausal or perimenopausal women.[7] This might be due to the fact that adipose tissue produces hormones (e.g., leptin, tumor necrosis factor) that inhibit ovarian steroid production. Thus, there was only a slight level of estrogen in obese women, and this led to the development of severe VMS. One other study of women aged 47–59 years demonstrated that a greater percentage of body fat was significantly associated with reporting of VMS.[4] A possible explanation for this may be that when the body's adipose tissue volume was increased, it provided a higher level of insulation, that was followed by higher body temperature and increasing VMS. In other words, aromatization was suppressed from high body temperature.[4] Another study of perimenopausal women aged 42-52 years examined the relationship between VMS and several factors, including hormone level measurement. The result showed that VMS was more common in women with high BMI.[5] There was no increase in estrogen level in obese women while increasing body fat provided more insulation which would increase core body temperature and thus might increase in hot flushes, and prevent aromatization in adipose tissue. A randomized trial in women aged 40-65 years showed that perimenopausal women with a BMI ≥25 kg/m^2 were more likely to report hot flushes than women with a BMI <25 kg/m^2 (OR: 2.00, 95% CI 1.28-3.12).[23] However, BMI was not associated with hot flushes in postmenopausal women. Some later studies reported similar results that obesity is associated with higher VMS prevalence during the midlife.[24-28]

Interestingly, some studies reported no association between BMI and VMS in postmenopausal women.[15,16] On the contrary, a cohort study of both premenopausal and postmenopausal women reported that the median duration of moderate to severe VMS was 10.2 years. That study also found that thinner women had longer duration of VMS than heavier weight women (BMI >30 kg/m^2, p =0.003).[6] That group postulated that women with heavier weight have higher estradiol levels than thinner women. Another later cross-sectional study of natural menopause women aged 40-60 years in factors related to VMS reported that thin and smoking women during the premenopausal period were more likely to experience VMS than obese women (p =0.03). However, from that study only BMI could not be the only factor that affected VMS.[11]

The results of this study showed results different from many previous studies. Perception of VMS may vary among ethnicities and countries, and the structured questions used to evaluate VMS may vary among studies. The design of the study (cross-sectional *vs.* cohort) and subject selection (perimenopausal *vs.* postmenopausal) may also affect the result since VMS may be perceived mostly during the perimenopausal period.

Limitation

VMS is subjective, self-reported, and there is no standard for measuring the level of VMS in individuals. Different patients perceive different levels of VMS. In other words, an individual's perception of VMS may not be estimated as the same level between reports, which makes it difficult to compare the level of symptoms. In order to answer our questionnaire, patients had to recall their recent symptoms during their firsts visit to our menopause clinic.

CONCLUSION

In this study population, Thai menopausal women with a normal BMI were significantly more likely to report moderate-to-severe VMS than postmenopausal women with higher BMI. This finding supports the hypothesis that heavier Thai women may have a higher level of estrogen due to aromatization in adipose tissue. These results suggest the need for more careful screening of under or normal weight women for VMS during menopause.

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Factors Associated with Xerostomia in Non-Radiated Patients

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ABSTRACT

Objective: To identify factors significantly associated with xerostomia in non-radiated patients.

Methods: Patients who attended the outpatient otolaryngology clinic at Siriraj Hospital (Bangkok, Thailand) with complaints of dry mouth were invited to join this study. Collected data included age, gender, body mass index, smoking status, alcohol use, underlying disease, and previous medication and/or therapy. Irradiated patients were excluded. Participants were classified into either the diseased or xerostomia group by abnormal oral cavity examination and symptoms, or the no xerostomia group, which was defined as dry mouth symptoms with no presence of abnormal physical findings.

Results: Two hundred and two participants with a history of dry mouth were consecutively enrolled. There were 86 patients with physical findings compatible with xerostomia, and 116 symptomatic patients without xerostomia. Multivariate analysis revealed age over 50 years (adjusted odds ratio [aOR]: 3.1, 95% confidence interval [CI]: 1.3-7.9; p=0.012), analgesic and muscle relaxant intake (aOR: 3.6, 95% CI: 1.3-9.7; p=0.012), psychotherapeutic medication (aOR: 7.8, 95% CI: 2.6-23.7; p<0.001), and radioactive iodine therapy (aOR: 3.7, 95% CI: 1.2-11.8; p=0.015) to be independent predictors of xerostomia.

Conclusion: Xerostomia is a condition that can adversely affect quality of life. The results of this study revealed older age (≥50 years), analgesics and muscle relaxants, psychotherapeutic medications, and radioactive iodine therapy to be significantly associated with xerostomia. A thorough understanding of the symptoms, diagnosis, relevant risk factors, and effective management is essential for improving outcomes among patients with xerostomia.

Keywords: Xerostomia; underlying disease; medication; non-radiation patients (Siriraj Med J 2019; 71: 377-384)

INTRODUCTION

Saliva plays an important role in oral health by helping to prevent infection, and by facilitating chewing, swallowing, and speaking. Xerostomia and salivary gland hypofunction are two terms that highlight the important relationship between saliva and oral health. However, no significant association between these two conditions has been reported. Some patients have salivary gland hypofunction without having xerostomia. However, it was reported that individuals with xerostomia may have abnormal or low flow of saliva.[1,2] Stimulated and non-stimulated saliva flow rates of <0.1 ml/min and <0.7 ml/min, respectively, are diagnosed as salivary gland hypofunction.[3] Xerostomia is a common subjective complaint of dryness in the mouth.[4] Defining xerostomia can be problematic and potentially confusing, because there are different questionnaires that use different criteria to identify xerostomia. Among the available questionnaire-based tools for diagnosing xerostomia, the Xerostomia Inventory is the most frequently used tool in a research setting. The Xerostomia Inventory is an 11-item tool that quantifies the severity of xerostomia.[5,6]

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Saliva has various roles and functions. First, it provides a defense against bacterial pathogens via enzymes, such as immunoglobulin A and lysozyme.[7,8] Second, it is an emulgent that aids enzymes that assist in the digestion of food. Third, saliva provides a physical glycoprotein and mucoid coating to prevent unfavorable substances from attaching to the teeth. This coating also aids in oral lubrication and swallowing.[9] Fourth, the bicarbonate and phosphate buffers in saliva help to maintain a neutral oral pH.[7] Therefore, patients that have xerostomia with either low or abnormal salivary flow are at high risk for developing oral health-related problems, such as dental caries, mucosal ulceration, oral candidiasis, and dysphagia – all of which can adversely impact quality of life.[10] It is, therefore, necessary for clinicians to understand the multidimensional aspects of this condition so that proper diagnosis can be made and proper treatment can be given in order to reduce complications and improve patient outcomes.

Xerostomia affects millions of people around the world. It is difficult to determine the exact prevalence of this condition; however, the prevalence was reported to range from 12% to 30%.[7] The most commonly reported cause of xerostomia is radiation to the head and neck region. Other possible causes that have been reported include medications and some specific diseases.[11-13]

Improved understanding of the factors that significantly associate with xerostomia will improve our understanding of this condition, and improve diagnosis, treatment, and outcomes. Accordingly, the aim of this study was to identify factors significantly associated with xerostomia in non-radiated patients that presented with dry mouth symptoms at Siriraj Hospital – Thailand's largest national tertiary referral hospital.

MATERIALS AND METHODS

Study design and population

The protocol for this prospective cross-sectional study was approved by the Siriraj Institution Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 512/2016). We consecutively recruited two hundred and two participants aged >18 years with symptomatic dry mouth from the outpatient clinic of the Department of Otorhinolaryngology during the September 2016 to December 2017 study period. Patients satisfying one or more of the following criteria were excluded: 1) declined to participate in the study; 2) unable to answer the questionnaire; 3) unable to undergo the physical examination; and/or, 4) had history of radiation therapy or chemotherapy at the head and/or neck.

Data collection

Patients that complained of dry mouth were asked to take the five-question Xerostomia Inventory – Dutch Version.[5,6] If the patient reported having one or more of the five listed symptoms, the patient was invited to join the study. Written informed consent was obtained from all participating patients. Clinical history to taken and physical examination was performed. Information that was collected included age, gender, body mass index, smoking status, alcohol use, medications, and current medical status. Using this information and the results of the physical examination, participants were allocated to either the diseased or xerostomia group[12,14] (defined as patients who had history of dry mouth with physical examination that revealed abnormal oral cavity) or the no xerostomia group (defined as having symptoms of dry mouth, but with no presence of abnormal physical findings) (Fig 1).

Statistical analysis

SPSS statistics version 18 (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses. Descriptive statistics were used to summarize patient demographic and clinical data. Data are presented as frequency and proportion. Univariate analysis using chi-square test of independence was performed to evaluate association between investigated variables and xerostomia. Variables with a p-value <0.2 in univariate analysis were included in multivariate analysis using logistic regression model. The results of multivariate analysis are presented as odds ratio (OR) with 95% confidence interval (CI) and adjusted OR (aOR) with 95% CI. A p-value <0.05 indicates statistical significance.

RESULTS

The study population comprised 202 participants with complaint of dry mouth, and the age range of patients was 19-81 years. Eighty-six participants were allocated to the xerostomia group, and 116 participants were assigned to the no xerostomia group. The mean age of patients was 63.30±11.26 years in the xerostomia group, and 57.44±14.7 years in the no xerostomia group. Among the entire study cohort, 57 (28.2%) participants were male and 145 (71.8%) were female.

As shown in Table 1, significantly more patients in the xerostomia group acknowledged having the symptoms listed on the self-report questionnaire than patients in the no xerostomia group for all 5 of the listed symptoms (all p<0.001). "My mouth feels dry" (87%) and "My lips feel dry" (77%) were the two most commonly reported symptoms.

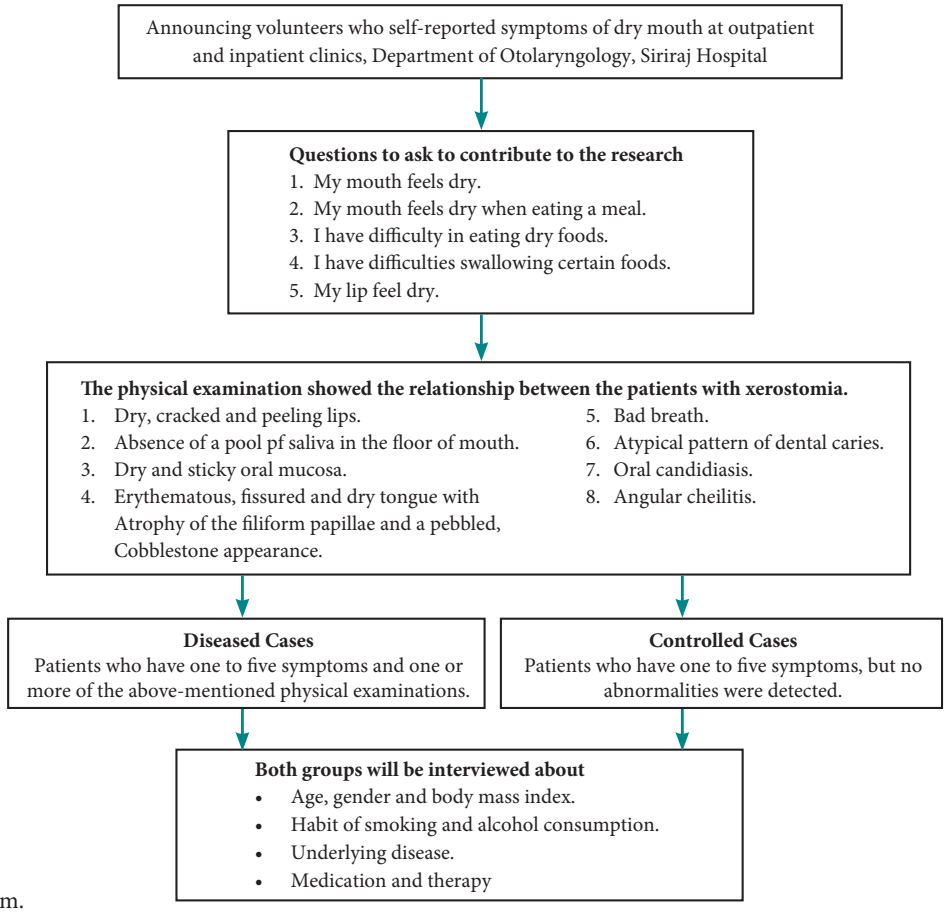


Fig 1. Flow diagram.

TABLE 1. Patient-reported symptoms.

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
My mouth feels dry	75 (87.2)	75 (64.7)	3.7 (1.8-7.8)	< 0.001**
My mouth feels dry when eating a meal	15 (17.4)	2 (1.7)	12.0 (2.7-54.2)	< 0.001**
I have difficulty in eating dry foods	21 (24.4)	3 (2.6)	12.2 (3.5-42.4)	< 0.001**
I have difficulties swallowing certain foods	26 (30.2)	7 (6.0)	6.7 (2.8-16.5)	< 0.001**
My lips feel dry	66 (76.7)	39 (33.6)	6.5 (3.5-12.3)	< 0.001**

**P<0.05: statistical significant

Fig 2 illustrates the results of various physical examinations in the xerostomia group. The most common findings from physical examination in the xerostomia group were lack of a saliva pool in the floor of the mouth (61.6%); presence of erythematous, fissured, and dry tongue with atrophy of the filiform papillae, and a pebbled cobblestone appearance (58.1%); dry, cracked, and peeling lips (50.0%); and, dry and sticky oral mucosa (48.8%).

Univariate analysis revealed the prevalence of xerostomia to be significantly increased in the ≥50 age group compared to the 0-49 age group (odds ratio [OR]: 2.9, 95% confidence interval [CI]: 1.3-6.7; p=0.006). There were no significant differences between the xerostomia and no xerostomia groups for gender, body mass index, smoking status, or alcohol consumption. Univariate analysis for association between xerostomia with underlying

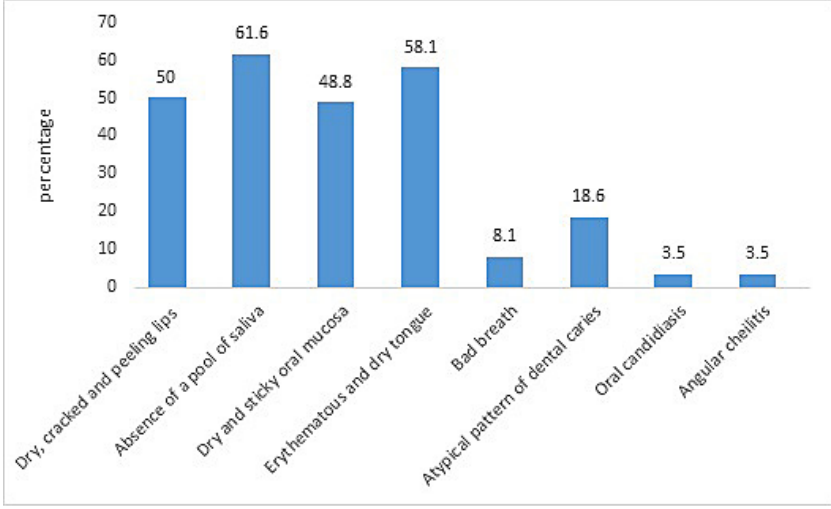


Fig 2. Prevalence of physical examination in xerostomia group.

disease, medications and therapies is presented in Table 3. Factors with a *p*-value <0.2 in univariate analysis and factors of interest were included in multivariate analysis.

Multivariate analysis revealed age ≥50 years (adjusted OR [aOR]: 3.1, 95% CI: 1.3-7.9; *p*=0.012), analgesic and muscle relaxant medication (NSAIDs, gabapentin) (aOR: 3.6, 95% CI: 1.3-9.7; *p*=0.012), psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic) (aOR: 7.8, 95% CI: 2.6-23.7; *p*<0.001), and radioactive iodine therapy (131I) (aOR: 3.7, 95% CI: 1.2-11.8; *p*=0.015) to be independent predictors of xerostomia (Table 4).

TABLE 2. Univariable analysis of associations with xerostomia (Age group, Gender, BMI, Smoking and Alcohol consumption).

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
Age category				
0-49	9 (10.5)	30 (25.9)	1.0	0.006*
≥50	77 (89.5)	86 (74.1)	2.9 (1.3-6.7)	
Gender				
Male	18 (20.9)	39 (33.6)	1.0	0.058*
Female	68 (79.1)	77 (66.4)	1.9 (1.0-3.6)	
BMI				
0-22.99	41 (47.7)	53 (45.7)	1.0	0.887
≥23	45 (52.3)	63 (54.3)	0.9 (0.5-1.6)	
Smoking				
Never/former	85 (98.8)	114 (98.3)	1.0	1.000
Current	1 (1.2)	2 (1.7)	0.7 (0.1-7.5)	
Alcohol consumption				
Never/former	85 (98.8)	110 (94.8)	1.0	0.242
Current	1 (1.2)	6 (5.2)	0.2 (0.0-1.8)	

*P-value less than 0.2 will be selected for multivariable analysis
Abbreviation: BMI= Body mass index

TABLE 3. Univariable analysis of associations with xerostomia (underlying disease, medication and therapy).

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
Diabetes mellitus	20 (23.3)	19 (16.4)	1.5 (0.8-3.1)	0.279
Hypertension	41 (47.7)	45 (38.8)	1.4 (0.8-2.5)	0.250
Cardiovascular disorders	6 (7.0)	3 (2.6)	2.8 (0.7-11.6)	0.174
Thyroid disorders	19 (22.1)	35 (30.2)	0.7 (0.3-1.3)	0.260
Psychological disorders	13 (15.1)	1 (0.9)	20.5 (2.6-159.9)	< 0.001**
Neurological disorders	6 (7.0)	8 (6.9)	1.0 (0.3-3.0)	1.000
Rhinitis	13 (15.1)	25 (21.6)	0.6 (0.3-1.3)	0.278
Autoimmune disorders	4 (4.7)	2 (1.7)	2.8 (4.5-15.5)	0.405
Respiratory disorders	3 (3.5)	7 (6.0)	0.6 (0.1-2.2)	0.522
Dyslipidemia	33 (38.4)	41 (35.3)	1.1 (0.6-2.2)	0.768
Skeletal disorders	12 (14.0)	7 (6.0)	2.5 (0.9-6.7)	0.086
Hematologic disorders	0 (0.0)	2 (1.7)	0.6 (0.5-0.6)	0.509
Extraesophageal symptoms	5 (5.8)	4 (3.4)	1.7 (0.5-6.6)	0.500
Renal disorders	1 (1.2)	3 (2.6)	0.4 (0.0-4.3)	0.638
Gastrointestinal disorders	5 (5.8)	4 (3.4)	1.7 (0.4-6.6)	0.500
Antihypertensive medication	41 (47.7)	49 (42.2)	1.2 (0.7-2.1)	0.476
Endocrinologic medication	38 (44.2)	42 (36.2)	1.4 (0.8-2.5)	0.309
Analgesic and muscle relaxant medication (NSAIDs, gabapentin)	16 (18.6)	7 (6.0)	3.6 (1.4-9.1)	0.007*
Antihistamine	14 (16.3)	24 (20.7)	0.7 (0.4-0.5)	0.471
Psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic)	18 (20.9)	5 (4.3)	5.9 (2.1-16.1)	< 0.001*
Antiplatelet (aspirin, clopidogrel)	16 (18.6)	8 (6.9)	3.1 (1.3-7.6)	0.015*
Anticoagulation	1 (1.2)	3 (2.6)	0.4 (0.0-4.3)	0.638
Respiratory medication	4 (4.7)	3 (2.6)	1.8 (0.4-8.4)	0.462
Antidyslipidemia	34 (39.5)	37 (31.9)	1.4 (2.8-2.5)	0.298
Gastrointestinal medication (prokinetic, laxative)	5 (5.8)	2 (1.7)	3.5 (0.7-18.6)	0.138*
Proton pump inhibitor	13 (15.1)	6 (5.2)	2.8 (1.1-7.3)	0.041*
Nutritional medication	21 (24.4)	23 (19.8)	1.3 (0.7-2.6)	0.492
Neurological medication	2 (2.3)	2 (1.7)	1.4 (0.2-9.8)	1.000
Cardiovascular medication	2 (2.3)	1 (0.9)	2.7 (0.2-30.7)	0.576
Immunosuppressant medication	1 (1.2)	1 (0.9)	1.3 (0.1-21.9)	1.000
Radioactive Iodine therapy (^{131}I)	9 (10.5)	6 (5.2)	2.1 (0.7-6.3)	0.181*

*P-value less than 0.2 will be selected for multivariable analysis, **P<0.05: statistical significant

TABLE 4. Factors associated with xerostomia, using multivariate analysis.

Factors	Crude Odds Ratio (95%CI)	Adjusted Odds ratio (95%CI)	*P*-value
Age (years)			
0-49	1.0	1.0	0.012**
≥50	2.9 (1.3-6.7)	3.1 (1.3-7.9)	
Gender			
Male	1.0	1.0	0.075
Female	1.9 (1.0-3.6)	1.9 (0.9-4.0)	
Analgesic and muscle relaxant medication (NSAIDs, gabapentin)	3.6 (1.4-9.1)	3.6 (1.3-9.7)	0.012**
Psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic)	5.9 (2.1-16.1)	7.8 (2.6-23.7)	< 0.001**
Antiplatelet (aspirin, clopidogrel)	3.1 (1.3- 7.6)	2.6 (0.9-7.2)	0.064
Gastrointestinal medication (prokinetic, laxatives)	3.5 (0.7-18.6)	2.8 (0.4-18.2)	0.283
Proton pump inhibitor	2.8 (1.1-7.3)	2.5 (0.7-8.3)	0.117
Radioactive Iodine therapy (^{131}I)	2.1 (0.7-6.3)	3.7 (1.2-11.8)	0.015**

**P<0.05: statistical significant

DISCUSSION

This study investigated the risk factors associated with xerostomia in non-radiated patients. A systemic review conducted by Tanasiewicz M, *et al.*[7] revealed a prevalence of xerostomia in population-based studies that ranged from 12% to 30%, with the wide range explained by differences in the assessment methods used among studies. There was no universal assessment available to compare xerostomia among those studies. Several different questionnaires for diagnosing xerostomia have been developed. A frequently used questionnaire in research is the 11-item Xerostomia Inventory.[1,2,15,16] The Xerostomia Inventory-Dutch Version is an abbreviated version of the original version that includes only the following 5 items: "My mouth feels dry", "My mouth feels dry when eating a meal", "I have difficulty in eating dry foods", "I have difficulties swallowing certain foods", and "My lips feel dry". The fact that the modified version has targeted statements/questions improved the validity of this version compared to the original version.[5,6] In the present study, we used this 5-item version and clinical examination to diagnose xerostomia. The positive oral findings include abnormal lips (dry, cracked, and peeling), absence of a saliva pool in the floor of mouth, dry and sticky oral mucosa, abnormal tongue (erythematous, fissured, and dry with atrophy of the filiform papillae, and a pebbled, cobblestone appearance), bad breath, atypical pattern of dental caries, oral candidiasis, and angular cheilitis. We found that significantly more patients in the xerostomia group reported each of the five items when compared to the no xerostomia group (all $p<0.001$). In addition, the following two items were reported by more 80% of patients: "My mouth feels dry when eating a meal" and "I have difficulty in eating dry foods".

In contrast to salivary gland hypofunction, which can be objectively evaluated using sialometry, the measurement of xerostomia remains problematic. Despite no distinctive relationship with hyposalivation, xerostomia is a critical symptom in oral health among clinicians, because it affects both oral health, general health, and quality of life.[8] Our opinion that xerostomia can significantly adversely affect patient quality of life was our motivation to investigate the factors that significantly associate with this important condition.

Oral mucosal lesions that were commonly found in this study were dry, cracked, and peeling lips. We also observed no presence of a saliva pool in the floor of mouth, dry and sticky oral mucosa, erythematous, and fissured

and dry tongue with atrophy of the filiform papillae and a pebbled, cobblestone appearance. Changes of the tongue surface may have both local (salivary gland hypofunction, inflammation, and changes in microcirculation) and systemic (disease and medication intake) pathogenic factors in common.[3,12]

In this study, we found significant association between age ≥50 years and xerostomia in multivariate analysis. This same finding was reported from several previous studies.[7-9,14,17] These results may also be caused by higher medication intake among older adults, with acini atrophy often found in patients with decreased output function.[15,18] The average age that menopause begins among females in Thailand was reported to be 49.5±3.6 years.[19]

A higher prevalence of xerostomia was observed in females than in males in the present study, but there was no statistically significant difference between genders, which is similar to the results reported from other studies.[20,21] However, significant association between gender and xerostomia was observed in most studies. Menopause in women could also affect the amount and characteristics of saliva.[9,22,23] It is also likely that females have to endure a higher level of pain intensity, and they may have more illness conditions that could lead to the development of xerostomia.[24] Other factors, including body mass index, tobacco use, and alcohol consumption, were found not to be associated with xerostomia.

Of note, xerostomia tends to markedly increase in patients with psychological disorders. Unstable emotions and changes in personality may play a role in xerostomia, with changes that can influence the nervous, immune, and endocrine systems. Moreover, anti-sialogic effects were observed in those taking drugs.[17,25]

In this study, multivariate analysis revealed significant associations between xerostomia and medications or therapy, including analgesic NSAIDs, gabapentin, muscle relaxants, psychotherapeutic drugs, and radioactive iodine therapy. Despite the fact that some of the mechanisms remain unknown, medication-induced xerostomia is commonly caused by the altering of neural pathways that stimulate the secretion of saliva.[10] Villa A, *et al.*[10] showed that patients taking analgesic medication (NSAIDs), and Scully C, *et al.*[26] reported that muscle relaxant medication, which blocks sodium and calcium channels, could be associated with significant xerostomia.

Psychotherapeutic medications in our study included antidepressants (tricyclic antidepressant and selective serotonin-reuptake inhibitor), anxiolytics, and antipsychotics. Tricyclic antidepressant (TCA) acts as a noradrenaline and serotonin stimulator by blocking their reuptake at the neuronal membrane. The block is also to histaminic, a1-adrenergic, and muscarinic cholinergic receptors, which can cause unfavorable drug reactions like xerostomia. Even though xerostomia can result from selective serotonin-reuptake inhibitor (SSRIs), they are less likely to cause anticholinergic side effects than TCA.[22,27] Anxiolytics and antipsychotics are also prone to cause xerostomia.[11]

We also found radioactive iodine therapy to be a factor significantly associated with xerostomia. Accumulation of radioactive iodine (131I) inflicts damage to the salivary gland, which can cause long-term complications. Qualitative and quantitative scintigraphy of salivary gland can be helpful for assessment and follow-up of salivary gland dysfunction after radioactive iodine therapy.[28-30]

Future studies should investigate whether drug dosage plays a role in the development of xerostomia, and comparative studies with a larger sample size would be required to make a clear distinction. Study in animals may also help us to elucidate the pathophysiology of some common medications and their association with xerostomia (e.g., NSAIDs).

CONCLUSION

Xerostomia is a condition that can adversely affect quality of life. The results of this study revealed older age, analgesics and muscle relaxants, psychotherapeutic medications, and radioactive iodine therapy to be significantly associated with xerostomia. A thorough understanding of the symptoms, diagnosis, relevant risk factors, and effective management is essential for improving outcomes among patients with this condition.

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Correlation Between CT Findings of Invasive Pulmonary Aspergillosis and Severity of Neutropenia

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ABSTRACT

Objective: The purpose of this study was to investigate the association between CT findings of invasive pulmonary aspergillosis and neutrophils level.

Methods: This retrospective study included the patients diagnosed with invasive pulmonary aspergillosis by computed tomography (CT) at Siriraj Hospital (Bangkok, Thailand) during May 2006 to May 2010. The patients were classified into two groups: group I = neutrophils <500 cells/mm^3, and group II = neutrophils ≥500 cells/mm^3. Patient demographic and clinical data were collected. CT findings were compared between groups, including consolidation, pulmonary nodule, pulmonary mass, centrilobular nodule, CT halo sign, CT hypodense, air crescent, central cavity, lymphadenopathy, and pleural effusion.

Results: Of the 43 patients that were included, 14 patients were assigned to group I, and 29 patients were allocated to group II. The mean age of patients was 40.2 years, and 48.8% were male. The most common CT finding of invasive pulmonary aspergillosis was pulmonary nodules (83.7%), followed by CT halo sign (76.7%) and consolidation (69.7%). The CT finding that showed significantly more commonly in patients in group I and group II was consolidation (p=0.02) and central cavity (p=0.03), respectively.

Conclusion: Consolidation was the CT finding significantly most commonly observed in invasive pulmonary aspergillosis with neutrophils <500 cell/mm^3, and central cavity was the finding significantly most commonly found in patients with neutrophils ≥500 cell/mm^3 with non-specific distribution.

Keywords: Aspergillosis; neutropenia; CT scan; lung; pulmonary (Siriraj Med J 2019; 71: 385-391)

INTRODUCTION

Aspergillus spp. are filamentous fungi that are acquired via the inhalation of spores. Pulmonary aspergillosis has 4 types, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, semi-invasive pulmonary aspergillosis, and invasive pulmonary aspergillosis. Each type of pulmonary aspergillosis depends on host immunity.[1,2] Invasive pulmonary aspergillosis is a major complication in immunocompromised patients. Major risk factors for invasive pulmonary aspergillosis infection include prolonged neutropenia (<500 cells/mm^3 for >10 days) or neutrophil dysfunction, post-transplantation, prolonged (>3 weeks) and high-dose corticosteroid therapy, hematological malignancy (e.g., leukemia), cytotoxic therapy, and advanced AIDS.[1,3]

Neutrophils are the dominant host defense against fungi by their action as natural killer cells that are recruited to the lungs by chemokines. They aggregate around conidia in the airways to prevent their germination.[4,5] Neutropenia for more than 10 days is the most important risk for invasive pulmonary aspergillosis. In addition, invasive pulmonary aspergillosis is related to the duration and

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degree of neutropenia. The risk of invasive pulmonary aspergillosis in neutropenic patients was estimated to be 1% per day for the first 3 weeks.[1]

Diagnosis of invasive pulmonary aspergillosis is made by clinical findings, physical examination, laboratory markers (polymerase chain reaction, galactomannan testing), sputum or bronchoalveolar lavage fluid culture, histopathology, and radiologic findings. The clinical presentation of invasive pulmonary aspergillosis is usually non-specific, such as fever, clinical unresponsive to antibiotics, chest pain, hemoptysis, and productive cough.[6,7] Early diagnosis of invasive pulmonary aspergillosis is necessary in these patients because the outcome depends on early treatment with an appropriate antifungal drug. Computed tomography (CT) chest imaging is an important diagnostic tool for early diagnosis.[8]

Chest radiograph is not sufficiently sensitive for the diagnosis of invasive pulmonary aspergillosis. Plain chest radiograph may exhibit non-specific nodular opacities or air-space infiltration in early phase. However, the air crescent sign and cavitation may become visible on chest radiographs in later stage.[2,6]

Thoracic CT scan is the most sensitive investigation for early detection of invasive pulmonary aspergillosis. Thoracic CT should be performed in neutropenic patients with fever that are not responding to antibiotics.[6] The gold standard investigation for diagnosis of invasive pulmonary aspergillosis is histological or pathological examination of lung tissue from needle aspiration or biopsy. However, these procedures are invasive, and they are associated with an increased risk of bleeding. As a result, thoracic CT scan is considered to be much more useful method for early diagnosis, and it has a prognostic impact on the outcome by detection of early disease.

CT findings of invasive pulmonary aspergillosis are variable. Findings that might be observed include CT halo sign (consisting of a central nodule, mass, or consolidation surrounded by a zone of hemorrhage that is found in the early phase of disease), crescentation or central cavity sign (develops days to weeks after the initial presentation, or in the resolving phase of the infection when neutropenia in the peripheral blood is increasing), CT hypodense sign (consisting of central low-density area within nodule or consolidation caused by vascular obstruction with secondary lung infarction), and non-specific nodular opacities or air space infiltration in the early stage of infection.[2,8,9]

The aim of this study was to identify association between thoracic CT findings of invasive pulmonary aspergillosis and serum neutrophil level.

MATERIALS AND METHODS

Subjects

All patients aged greater than 15 years with diagnosis of invasive pulmonary aspergillosis who underwent thin-section thoracic CT scan at the Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during May 2006 to May 2010 were retrospectively reviewed. Patients diagnosed with proven, probable, or possible invasive pulmonary aspergillosis according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were included.[3] The protocol for this study was approved by the Siriraj Institutional Review Board (Si 180/2011).

Serum neutrophil level and clinical data (age, underlying diseases, presenting symptoms, laboratory investigation, time interval from clinical onset to CT findings, and histological or pathological report) of all individuals were collected from our center's electronic medical record database. Regarding serum neutrophil level, patients were classified into either group I (neutrophils <500 cells/mm^3) or group II (neutrophils ≥500 cells/mm^3).

Imaging and imaging interpretation

CT examinations were obtained with a 64-slice multi-detector row CT (GE or Siemens). The GE parameters were 120 kVp, 250 mA, and pitch = 1.375 craniocaudal, and the Siemens parameters were 120 kVp, 250 mA, and pitch = 0.8 craniocaudal. Spiral CT scan was obtained during full inspiration with or without contrast media administration.

The CT findings were assessed by two radiologists, and conclusions were reached by consensus. The pattern of pulmonary abnormality findings, associated findings, and distribution was analyzed. The pulmonary abnormality findings were consolidation (area of increase in pulmonary parenchymal attenuation that obscures the margin of vessels and airway wall), pulmonary nodule (round opacity lesion, ≤3 cm in diameter), pulmonary mass (round pulmonary opacity >3 cm in diameter), and centrilobular nodule (small opacity in the center of a secondary pulmonary lobule).[10] The associated findings were "CT halo sign" (ground-glass attenuation surrounding a pulmonary nodule or consolidation) (Fig 1), CT hypodense sign (the differences between lung opacity in the peripheral zone of the lesion and lower density of necrotic central area >15 HU in mediastinal window setting) (Fig 2), air

crescent sign (crescent shaped area of air density within pulmonary nodule or mass) (Fig 3), central cavity (a lucent area of air density within an area of consolidation, nodule, or mass) (Fig 4), lymphadenopathy, and pleural effusion.[8]

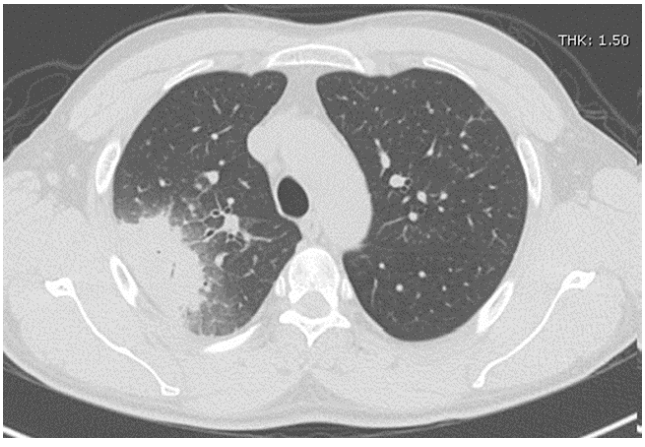


Fig 1. A 40-year-old male with underlying acute aplastic anemia and neutrophils 28 cells/mm^3 presented with fever and cough. Axial thoracic CT scan demonstrated pulmonary consolidation surrounded with ground-glass opacity at right upper lobe that represented CT halo sign. The final diagnosis was invasive pulmonary aspergillosis.

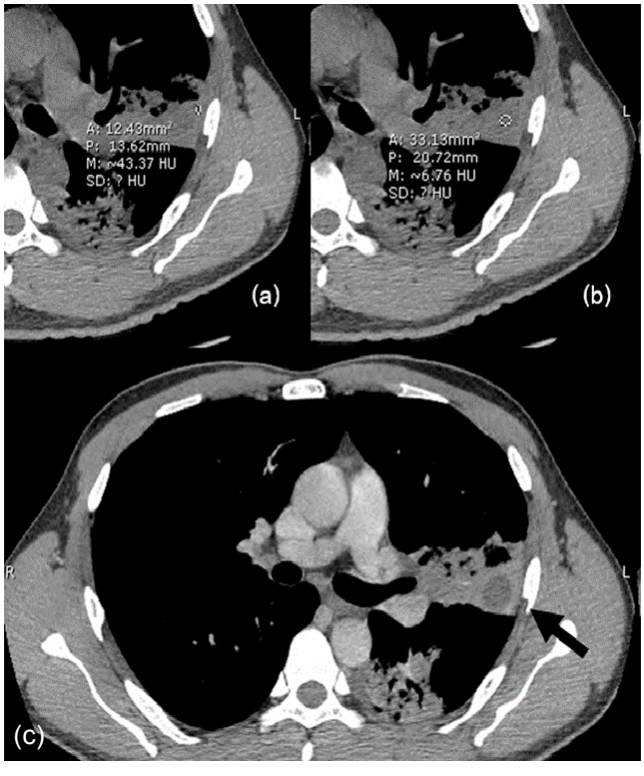


Fig 2. A 32-year-old male with underlying acute myeloblastic leukemia and neutrophils 1,761 cells/mm^3 presented with fever. (a, b) axial unenhanced thoracic CT scan demonstrated two consolidation areas at left upper lobe. One of them showed differences in lung opacity in the peripheral zone of the lesion (43.3 HU in a), and lower density of necrotic central areas (6.7 HU in b) that represented CT hypodense sign. (c) axial post-contrast-enhanced thoracic CT confirmed CT hypodense sign (arrow). The final diagnosis was invasive pulmonary aspergillosis.



Fig 3. A 27-year-old female with underlying acute myeloblastic leukemia and neutrophils 3,171 cells/mm^3 presented with fever. Axial thoracic CT scan demonstrated a crescent shaped area within an area of consolidation that represented air crescent sign at right upper lobe. Ground-glass nodules at left upper lobe were also noted. The final diagnosis was invasive pulmonary aspergillosis.

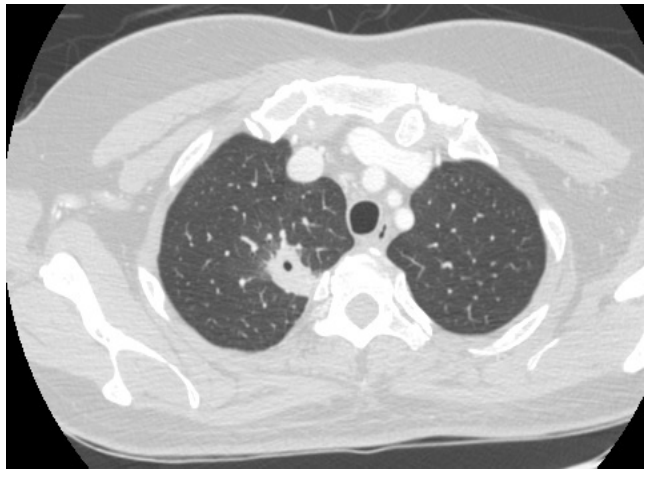


Fig 4. A 53-year-old male with underlying acute myeloblastic leukemia and neutrophils 1,159 cells/mm^3 with history of fever and cough. Axial thoracic CT scan demonstrated a lucent area within nodule that represented central cavity at right upper lobe. The final diagnosis was invasive pulmonary aspergillosis.

Statistical analysis

The age of patients and duration from imaging to CBC examination are expressed as mean. All qualitative data, including gender, different criteria for diagnosis of invasive pulmonary aspergillosis, and CT findings, are described as frequency and percentage. Chi-square test was used to analyze the radiographic findings, and to examine for correlation between 2 groups of CT findings and neutrophil levels. A *p*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using a statistical software package (SPSS Statistics version 13.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

The characteristics of 43 patients with diagnosis of invasive pulmonary aspergillosis by proven (6.9%), probable (20.9%), and possible (72.0%) criteria are summarized in Table 1. Patients were classified into 2 groups. Fourteen patients (32.6%) were classified in group I (serum neutrophil level <500 cell/mm^3), and 29 patients (67.4%) were classified in group II (serum neutrophil level ≥500 cell/mm^3). The mean age of patients in group I (40.7 years) was not significantly different from that of group II (39.9 years). The gender distribution was similar in each of the 2 groups (group I: 7 males and 7 females vs. group II: 14 males and 15 females). The mean time interval from the date of thoracic CT scan to CBC was 0.7 days in group I, and 0.6 days in group II (p>0.05). The mean time interval from clinical onset to CT findings was 9.9 days in group I, and 13.2 days in group II (p>0.05). The underlying diseases in group I were aplastic anemia (21.4%), acute lymphoblastic leukemia (21.4%), acute myeloid leukemia (35.7%), chronic myeloid leukemia (14.3%), and unspecified neutropenia (7.1%). The underlying diseases in group II were acute lymphoblastic leukemia (20.7%), acute myeloid leukemia (58.6%), chronic myeloid leukemia (3.4%), lymphoma (13.8%), and systemic lupus erythematosus (3.4%).

CT protocol

There were 38 CT studies (87.7%) performed with contrast medium administration, and 5 studies (12.3%) performed without contrast medium administration. Regarding slice thickness of the CT scan, 0.6 mm was used in 5 studies (10.8%), 0.63 mm in 7 studies (16.9%), 1.25 mm in 16 studies (36.9%), 1.5 mm in 13 studies (30.8%), and 4 mm in 2 studies (4.6%).

Imaging interpretation

CT findings of invasive pulmonary aspergillosis and associated findings were assessed for the following radiological patterns; consolidation, pulmonary nodule, pulmonary mass, centrilobular nodule, CT halo sign, CT hypodense sign, air crescent, central cavity, lymphadenopathy, and pleural effusion. The prevalence of each of these finding was compared between groups (Table 2).

TABLE 1. Patient demographic and clinical characteristics.

Characteristics	Neutrophils <500 cells/mm^3	Neutrophils ≥500 cells/mm^3	Total
Number, n (%)	14 (32.6%)	29 (67.4%)	(N=43)
Age (mean)	40.7 years	39.9 years	40.2 years
Gender, n (%)			
Male	7	14	21 (48.8%)
Female	7	15	22 (51.2%)
Criteria diagnosis, n (%)			
Proven IPA	1 (7.1%)	2 (6.9%)	3 (7.0%)
Probable IPA	4 (28.6%)	5 (17.2%)	9 (20.9%)
Possible IPA	9 (64.3%)	22 (75.9%)	31 (72.1%)
Duration from imaging to CBC (mean)	0.7 days	0.6 days	0.7 days
Underlying conditions, n (%)			
Aplastic anemia	3 (21.4%)	0 (0.0%)	3 (7.0%)
ALL	3 (21.4%)	6 (20.7%)	9 (20.9%)
AML	5 (35.7%)	17 (58.6%)	22 (51.2%)
CML	2 (14.3%)	1 (3.4%)	3 (7.0%)
Lymphoma	0 (0.0%)	4 (13.8%)	4 (9.3%)
SLE	0 (0.0%)	1 (3.4%)	1 (2.3%)
Unspecified neutropenia	1 (7.1%)	0 (0.0%)	1 (2.3%)

Abbreviations: IPA=invasive pulmonary aspergillosis; CBC=complete blood count; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CML=chronic myeloid leukemia, SLE=systemic lupus erythematosus

TABLE 2. Computed tomography (CT) findings and associated findings of invasive pulmonary aspergillosis compared between neutrophil levels.

CT findings	Neutrophils <500 cells/mm³	Neutrophils ≥500 cells/mm³	Total	P-value
Consolidation	13 (92.9%)	17 (58.6%)	30 (69.7%)	0.02
Nodule	11 (78.6%)	25 (86.2%)	36 (83.7%)	0.52
Mass	0 (0.0%)	1 (3.4%)	1 (2.3%)	0.48
Centrilobular nodule	1 (7.1%)	2 (6.9%)	3 (6.9%)	0.97
Associated findings	**Neutrophils <500 cells/mm³**	**Neutrophils ≥500 cells/mm³**	**Total**	**P-value**
Peripheral GGO (halo sign)	13 (69.9%)	20 (69.0%)	33 (76.7%)	0.08
CT hypodense sign	5 (35.7%)	13 (44.8%)	18 (41.8%)	0.57
Air crescent sign	1 (7.1%)	8 (27.6%)	9 (37.2%)	0.12
Central cavity	2 (14.3%)	14 (48.3%)	16 (37.2%)	0.03
Lymphadenopathy	3 (11.5%)	4 (13.8%)	7 (16.2%)	0.96
Pleural effusion	10 (71.4%)	12 (41.4%)	22 (51.1%)	0.06

A *p*-value <0.05 indicates statistical significance
Abbreviation: GGO=ground glass opacification

There was no significant difference in the pattern of pulmonary nodule (78.6% in group I vs. 86.2% in group II, *p*=0.52), pulmonary mass (0% in group I vs. 3.4% in group II, *p*=0.48), centrilobular nodule (7.1% in group I vs. 6.9% in group II, *p*=0.97), CT halo sign (69.9% in group I vs. 69.0% in group II, *p*=0.08), CT hypodense sign (35.7% in group I vs. 44.8% in group II, *p*=0.57), air crescent sign (7.1% in group I vs. 27.6% in group II, *p*=0.12), lymphadenopathy (11.5% in group I vs. 13.8% in group II, *p*=0.96) and pleural effusion (71.4% in group I vs. 41.4% in group II, *p*=0.96), as shown in Table 2.

Consolidation was the CT finding significantly more commonly found in group I than in group II (92.9% vs. 58.6%, respectively; *p*=0.02). Central cavity was the CT finding significantly more commonly observed in group II than in group I (48.3% vs. 14.3%, respectively; *p*=0.03).

The distribution of lesions was, as follows: right upper lobe (RUL) (83.7%), left upper lobe (LUL) (72.1%), right lower lobe (RLL) (69.8%), left lower lobe (LLL) (67.4%), and right middle lobe (RML) (48.8%).

DISCUSSION

Invasive pulmonary aspergillosis is a major cause of mortality in immunocompromised patients. Neutrophils and alveolar macrophages play important roles in killing conidia and developing hyphae. If abnormalities exist in these defense mechanisms, the conidia undergo germination and turn to invasive hyphae. As such, neutropenia status is a major risk factor for invasive pulmonary aspergillosis.[2,5] The clinical signs and symptoms of invasive pulmonary aspergillosis include fever, unresponsiveness to antibiotics, productive cough, dyspnea, haemoptysis, and pleuritic chest pain. Diagnosis of invasive pulmonary aspergillosis can be made by combining clinical, radiographic, laboratory, and histopathologic data. Thoracic CT scan has become an important tool for diagnosing invasive pulmonary aspergillosis due its non-invasive nature and its high sensitivity (>80%) and specificity (60-98%).[6]

Pathologically, Aspergillus spp. invades pulmonary blood vessels and cause hemorrhagic infarction. Characteristic early lesions consist of central areas of necrosis surrounded by a zone of hemorrhage, which

corresponds with the CT halo sign.[11,12] The process of cavitation characteristically results in the air crescent sign, which histologically represents necrotic lung mixed with hyphae and granulocytic infiltrate that is surrounded by a thin rim of air.[2,11,13]

Hyung Jin Won, *et al.* described CT findings in 5 patients with neutropenia (<500 cells/mm^3) and proven invasive pulmonary aspergillosis. Most common manifestation of invasive pulmonary aspergillosis was segmental area of consolidation with ground-glass appearance (i.e., CT halo sign) (n=4, 20%) and at least one nodule surrounded by a halo (n=2, 40%).[9] Kuhlman, *et al.* found the typical CT findings of invasive pulmonary aspergillosis to be multiple nodules or fluffy masses or consolidation with surrounding halos of low attenuation. Some form of cavitation or air crescent formation was found at or near the time of granulocyte recovery.[12] Horger, *et al.* found the CT hypodense sign in 13 of 43 patients (30.2%) with invasive pulmonary aspergillosis. Eleven patients (84.6%) had neutrophils <500 cells/mm^3 and 2 patients (15.4%) had neutrophils ≥500 cells/mm^3, and the CT hypodense sign was more common in patients with neutrophils <500 cells/mm^3. The CT hypodense sign showed an area of central necrosis and proved to be a precursor of the crescent sign within a range of 2-19 days.[8] Logan, *et al.* assessed the CT findings and pathological findings in invasive aspergillosis of the airways in 9 patients. Their result showed CT findings in patients with neutrophil level <500 cells/mm^3 (n=3) to be peribronchial consolidation, CT halo sign, and centrilobular micronodules. The CT findings in patients with neutrophil level ≥500 cells/mm^3 (n=6) were centrilobular micronodules, diffuse bronchiectasis, peribronchial consolidation, and diffuse ground-glass attenuation.[14] However, no previous study reported significant difference in the CT findings of invasive pulmonary aspergillosis patients compared between those with neutrophil level <500 cells/mm^3 and those with neutrophil level ≥500 cells/mm^3.

The present study found the most common CT finding of invasive pulmonary aspergillosis to be pulmonary nodules, followed by CT halo sign and consolidation. We classified patients into 2 groups (group I = neutrophil level <500 cells/mm^3, and group II = neutrophil level ≥500 cells/mm^3) and compared findings between groups. We found consolidation to be significantly more commonly observed in patients with neutrophil level <500 cell/mm^3. This is because the extent and severity of infection in patients depends on the degree of immunodeficiency and duration of neutropenia.[2] Invading fungi are more expanded in individuals with profound granulocytopenia, which results in a greater extent of infected infarction (consolidation). Central cavity was found significantly more often in patients with neutrophil level ≥500 cells/mm^3. This might be explained by the cavitating process of fungal nodules, which relies on granulocytic response. Fungal nodules in patients with granulocytic function defect or in patients who remain neutropenic do not cavitate.[2,15]

The most common CT finding of invasive pulmonary aspergillosis in the present study was presence of pulmonary nodule (36 of 43 cases [83.7%]), and the second most common finding was CT halo sign (33 of 43 cases [76.7%]). However, neither of these findings were statistically significantly different between groups. The other CT findings that showed no significant difference between groups were centrilobular nodule, pleural effusion, pulmonary mass, CT hypodense sign, air crescent sign, and lymphadenopathy. These lesions in this study showed no obvious prominence in any pulmonary lobes, which indicates non-specific distribution.

Limitations

This study has some mentionable limitations. First, the retrospective nature of our study made it difficult to control factors, such as CT protocol (with or without contrast, slice thickness) and duration from date of CT scan to date of CBC examination. Second, there were only 3 proven cases of invasive pulmonary aspergillosis by histology or cytopathology. This can be explained by the fact needle aspiration and lung biopsy are both invasive procedures that are associated with increased risk of bleeding in patients with a hematologic problem. Third, the size of our study population was relatively small and there was substantial asymmetry between groups. It is possible that these factors could have adversely influenced the results of our statistical analyses.

CONCLUSION

Consolidation was the CT finding significantly most commonly observed in invasive pulmonary aspergillosis with neutrophils <500 cell/mm^3, and central cavity was the finding significantly most commonly found in patients with neutrophils ≥500 cell/mm^3 with non-specific distribution.

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Success Rate of Cervical Cerclage at Siriraj Hospital

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ABSTRACT

Objective: To determine the success rate of cervical cerclage at Siriraj Hospital and the associated factors.

Methods: The study included 90 pregnant women who received cervical cerclage procedures at Siriraj Hospital during 2007-2016. Clinical information and the cerclage procedures were evaluated. Successful cervical cerclage was defined as delivery at 34 weeks' gestation or more.

Results: The mean maternal age was 31.8 ± 5 years. The most common indication was history of second trimester abortion (76.7%). The mean gestational age (GA) at cervical cerclage was 18.0 ± 4.3 weeks. The mean cervical length was 25.2 ± 12.0 mm. Most of the patients had no cervical dilatation (76.7%). Almost all the cervical cerclage procedures were performed using McDonald's technique (98.9%). Of the 90 women, 66 (73.3%) delivered at >34 weeks' gestation, while 59.9% delivered at >37 weeks' gestation. The mean birth weight was 2404.9 ± 991.7 grams. The success rate of cervical cerclage increased significantly among women with greater cervical length (28.2±10.5 vs. 18.0±14.9 mm., p=0.002), without cervical dilatation (83.3% vs. 58.3%, p=0.046), without bulging of membranes (92.5% vs. 66.7%, p=0.002), and prophylactic operations (89.4% vs. 58.3%, p=0.001). Maternal complications were significantly lower in women with successful cervical cerclage (9.1% vs. 45.8%, p<0.001).

Conclusion: The success rate of cervical cerclage at Siriraj Hospital was 73.3%. Possible associated factors included cervical length, cervical dilatation, bulging of membranes, and the prophylactic procedure.

Keywords: Cervical cerclage; success rate (Siriraj Med J 2019; 71: 392-398)

INTRODUCTION

Preterm delivery is the most significant obstetric problem worldwide and is a major cause of death after birth. Surviving newborns have high morbidity and mortality rates, both short-term and long-term complications such as neurological developmental abnormalities, respiratory distress, and visual and hearing problems. The issue incurs significant costs for healthcare services. In previous study, the incidence of preterm births in developed countries was found to be 5-7%, but this was higher in developing countries.[1] In Thailand, the incidence of preterm births was 12%,[2] similar to the rate at Siriraj Hospital (12.89%).[3]

Cervical insufficiency is a risk factor for preterm labour and is defined as the inability of the uterine cervix to retain a pregnancy in the absence of signs and symptoms of clinical contraction, labour, or both in the second trimester.[4] The incidence of cervical insufficiency is 0.12 - 2.0% in normal pregnancies, but 15% in habitual abortions.[5] The cause of cervical insufficiency is still unknown, although it is suspected to be related to cervical operative procedures such as conization, dilatation, and curettage. There is no criteria for diagnosis of cervical insufficiency. The diagnosis is dependent on cervical progression in the second trimester in the absence of

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labour pain or other causes such as premature rupture of membrane, bleeding from vagina, or infection. Transvaginal ultrasonography for cervical length measurement is now used to co-evaluate this condition. However, diagnosis of cervical insufficiency is not only based on short cervical length. Surgical and non-surgical procedures can be used to treat cervical insufficiency. For non-surgical treatments, physical activity restrictions, bedrest, and abstinence from sexual intercourse have been proposed but without strong supporting evidence.[6] Surgical treatment is in the form of the cervical cerclage procedure, which can be performed either transvaginally or transabdominally. McDonald and Shirodkar's techniques are considered standard cervical cerclage techniques, and there is currently no significant data to prove which technique is superior.[7-9] Transabdominal cervical cerclage may be used in cases of failed transvaginal cervical cerclage or if there is a history of trachelectomy.

The American College of Obstetricians and Gynecologists (ACOG) provide a number of recommended indications of cervical cerclage.[4] The first is dependent upon history (history of unexplained second trimester delivery without labour or abruptio placenta). Second, a physical examination (painless cervical dilation in the second trimester). While the third is based on ultrasonographic information (short cervical length <25 mm.) with a history of prior preterm birth. A previous study reported that cervical cerclage in women with cervical incompetence significantly decreased the incidence of preterm delivery prior to 33 weeks' gestation.[10] Limited data is available for rescue cervical cerclage and the success rate is unpredictable. Prior observational studies suggest that rescue cervical cerclage may be able to improve the neonatal outcomes, although there is insufficient data.[11]

At Siriraj Hospital, cervical cerclage is used as a surgical treatment for women with cervical incompetence. Yet there is limited clinical information about the success rate of cervical cerclage and neonatal outcomes. The primary objective of this study was subsequently to assess the success rate of cervical cerclage procedures at Siriraj Hospital. Meanwhile, pregnancy outcomes and potential associated factors were also evaluated.

MATERIALS AND METHODS

After approval from the Siriraj Institutional Review Board (Si 555/2017), this retrospective descriptive study was conducted at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital. The sample size was calculated based on an estimated success rate of 70%. At a 95% confidence level and with a 10% acceptability error, a sample size of at least 81 cases were required. A total of 90 pregnant women who had undergone a cervical cerclage procedure at the hospital based on any indications between 2007 and 2016 were included in this study. At Siriraj Hospital, the cervical cerclage procedure is performed based on the recommendations of the American College of Obstetricians and Gynecologists.

This study evaluated the clinical information, characteristics of the cerclage procedure, and pregnancy outcomes. Women with detected fetal anomalies, multifetal pregnancy, or who had terminated their pregnancies due to maternal or fatal indications were excluded. Data was obtained from medical records, which included the baseline clinical information, characteristics of the cerclage procedures, and the pregnancy outcomes. Successful cervical cerclage was defined as delivery at > 34 weeks' gestation. Non-viable delivery before 24 weeks' gestation was defined as abortion.

After performing the cervical cerclage procedure, all the patients were admitted for medical staff to closely monitor uterine contraction. If uterine contractions were detected, a tocolytic drug was administered intravenously. Daily vaginal progesterone (Utrogestan 200 mg) was given in some cases until 36 weeks' gestation. An oral nonsteroidal anti-inflammatory drug (ibuprofen 800-1,200 mg per day) was given three days after the operation. In most cases, an intravenous antibiotic (Cefoxitin 1g) was administered intraoperation. And then an oral cephalosporin (Cephalexin 2g per day) was administered for seven days. Post-operative complications such as uterine contraction, vaginal bleeding, cervical laceration, rupture of membrane, and chorioamnionitis were recorded among the study sample population.

Descriptive statistics, including the mean, median, standard deviation, number, and percentage were used to describe the various characteristics as appropriate. Comparisons between the groups were performed using the Student's *t*-test and the chi square test as appropriate. P values less than 0.05 were considered statistically significant.

RESULTS

A total of 90 pregnant women who had undergone a cervical cerclage procedure were included in this study. Table 1 shows the patient's baseline characteristics. The mean maternal age was 31.8 ± 5 years, while the majority of the patients were nulliparous (61.1%), and 88.9% had previously undergone at least one abortion. A history of second trimester abortion was found in 76.7%. Meanwhile, 7.8 % had a history of preterm delivery and 15.6% had previous cervical cerclage. Cervical cerclage was indicated by a physical examination in 18.9% of the

TABLE 1. Baseline characteristics of the patients (N=90).

Characteristics	Mean ± SD
Mean age ± SD (year)	31.8 ± 5.0
	N (%)
Parity	
0	55 (61.1)
1	30 (33.3)
2	5 (5.6)
Abortion	
0	10 (11.1)
1	26 (28.9)
≥ 2	54 (60)
Underlying disease	
No	70 (77.8)
Diabetes mellitus	5 (5.6)
Hypertension	4 (4.4)
Cervical pathology*	3 (3.3)
Others**	8 (8.9)
History-indicated cerclage	
History of abortion in 2nd trimester	69 (76.7)
History of preterm delivery	7 (7.8)
Previous cervical cerclage	14 (15.6)
Physical examination-indicated cerclage	17 (18.9)
Ultrasound-indicated cerclage	31 (34.4)
Previous cervical operation	27 (30)
No	63 (70)
Dilatation and curettage	24 (26.7)
LEEP***	3 (3.3)

* Cervical pathology: Cervical intraepithelial neoplasia, **Others: asthma, hyperthyroid, chronic hepatitis B, mitral stenosis , ***LEEP = Loop electrosurgical procedure

women, while an ultrasonographic examination was used to indicate cervical cerclage in 34.4% of the women. Among these women, 9 cases of cervical cerclage were indicated by both history and a physical examination. Finally, 26 cases had cervical cerclage indicated by both history and ultrasonographic examination.

The characteristics of the cerclage procedure is demonstrated in Table 2. The mean gestational age at the cervical cerclage procedure was 18.0 ± 4.3 weeks and the mean cervical length was 25.2 ± 12.0 mm. Most of the patients had no cervical dilatation (76.7%), while 6.7% had a cervical dilatation of >3 cm. Cervical cerclage was performed as a prophylactic procedure in 81.1% of the women, while 18.9% underwent rescue operations. Almost all the cervical cerclage procedures were performed using McDonald's technique, while only a single woman underwent the Shirodkar technique following the cervical intraepithelial neoplasia III status post loop electrosurgical excision procedure (CIN III S/P LEEP). Antibiotic prophylaxis was used during the procedure in 91.1% of the cases, and progesterone supplement was used in 50% of the cases. Vaginal progesterone was administered as a supplement after the cerclage procedure until 36 weeks' gestation.

TABLE 2. Characteristics of cerclage procedure (N=90).

Characteristics	Mean ± SD
Mean gestational age at cerclage (weeks)	18.0 ± 4.3
Mean cervical length (mm) (N=70)	25.2 ± 12.0
	N (%)
Cervical dilatation at cerclage	
No dilatation	69 (76.7)
1-2 cm	15 (16.7)
≥ 3 cm	6 (6.7)
Bulging of membranes	13 (14.4)
Type of cervical cerclage	
Prophylactic procedure	73 (81.1)
Rescue procedure	17 (18.9)
Antibiotic prophylaxis	82 (91.1)
Progesterone treatment	45 (50.0)

Table 3 shows the pregnancy outcomes of the women in this study. The mean gestational age (GA) at delivery was 33.9 ± 6.2 weeks. Meanwhile, 66 (73.3%) of the women delivered at > 34 weeks' gestation and 58.9% delivered at > 37 weeks' gestation. All newborns in this group survived and had good outcomes, with APGAR scores > 7 at 1 and 5 minutes after birth, meanwhile there were no NICU admissions. The median interval from cervical cerclage to delivery was 125 days. The mean birth weight was 2404.9 ± 991.7 g. Among the 24 women who delivered before 34 weeks' gestation, 12 had abortions, 2 were stillbirth, and 10 of this group of newborns survived. The lowest GA of the surviving newborns was 27 weeks with a birth weight of 810 g. In the prophylactic cervical cerclage group, 59 out of the 73 women (80.8%) delivered at > 34 weeks' gestation, while 64.3% delivered at > 37 weeks' gestation. In the rescue cervical cerclage group, 7 out of the 17 (41.2%) women delivered at > 34 weeks' gestation and 35.3% delivered at >37 weeks' gestation. Term newborns who were delivered from a rescue operation had cervical dilatation varying between 2-3 cm. The mean interval from cervical cerclage to delivery was very different between the prophylactic and the rescue groups. In the prophylactic group, the median interval was 143 days whereas it was 60 days for the rescue group.

Table 4 displays a comparison between the various characteristics of women who delivered at ≥ 34 and < 34 weeks' gestation. There were no significant differences between the two groups in terms of age and gestational age at cerclage. The mean cervical length in the women who delivered at ≥ 34 weeks' gestation was significantly higher than those who delivered at <34 weeks' gestation (28.2 ± 10.5 vs. 18.0 ± 14.9 mm., p=0.002). Cervical dilatation was significantly less among those who delivered at ≥ 34 weeks' gestation, with 83.3% having no cervical dilatation compared to only 58.3% with cervical dilation in the other group (p=0.046), while bulging of membranes was also significantly less common in those delivered at ≥34 weeks' gestation (7.6% vs. 33.3%, p=0.002). The prophylactic cerclage procedure was significantly more common in those delivered at ≥34 weeks' gestation (89.4% vs. 58.3%, p=0.001). There were no significant differences found between the use of antibiotic prophylaxis and progesterone supplementation. Finally, maternal complications were significantly higher among those delivered at <34 weeks' gestation, including uterine contractions, vaginal bleeding, rupture of membrane and other complications (p<0.001).

DISCUSSION

Cervical cerclage is a surgical treatment used for patients with cervical incompetence which aims to reduce the risks of miscarriage and preterm birth. Cervical cerclage procedures are performed to increase the strengthening of the cervix either to maintain pregnancy until term

TABLE 3. Pregnancy outcomes of the women in the study (N=90).

Pregnancy outcome	Mean ± SD
Gestational age at delivery (weeks)	33.9 ± 6.2
	N (%)
Gestational age at delivery	
<24 weeks	12 (13.3)
24-27^{+6} weeks	5 (5.6)
28-33^{+6} weeks	7 (7.8)
34-36^{+6} weeks	13 (14.4)
≥37 weeks	53 (58.9)
Mean birth weight (grams) (N=87)	2404.9 ± 991.7
< 1,000	13 (14.9)
1,000-1,999	13 (14.9)
2,000-2,999	33 (37.9)
3,000-3,999	28 (32.1)
Maternal complication	
Uterine contraction	11 (12.2)
Vaginal bleeding	2 (2.2)
Rupture of membrane	2 (2.2)
Others**	2 (2.2)
	Median (IQR)
Interval from cerclage to delivery (days)	125 (63.8, 155.8)

*Others: cervical tear, chorioamnionitis

or to prolong the pregnancy for as long as possible. Based on previous studies,[12,13] there is limited clinical information about the procedures' efficacy and success rate, as well as regarding which patient groups benefit from the operation and the neonatal outcomes. The overall success rate in both the prophylaxis and rescue cervical cerclage groups in this study was 73.3% and there were good neonatal outcomes. The mean cervical length in the successful group (delivery at GA >34 weeks) was significantly higher than the other group. Cervical dilatation and bulging of membranes were significantly less in the successful group, similar to previous findings.[11,14] There were no significant differences between the cervical cerclage techniques, the use of antibiotic prophylaxis, and progesterone supplementation. Many studies support a similar efficacy between the McDonald and Shirodkar techniques.[7,9,15] McDonald's technique is found to be preferable since it is easier to place and remove the sutures. From a previous study, the addition of vaginal progesterone in the rescue cervical cerclage procedure was associated with a reduction of spontaneous preterm births.[16] Maternal complications were significantly higher among those delivered at <34 weeks' gestation, including uterine contractions, vaginal bleeding, and rupture of membranes.

Prophylactic cervical cerclage was performed in history-indicated and ultrasound-indicated patients. The results show that this group's success rate was high (80.8%) and with low levels of complications. For the rescue cervical cerclage procedure, the success rate was difficult to predict and usually had poor pregnancy outcomes. Patients who had a cervical dilatation exceeding 4 cm with bulging of fetal membrane into the vagina had a higher chance of cerclage failure.[17] In this study, the success rate in the rescue cervical cerclage procedure was only 41.2%. There was a case report of rescue cervical

TABLE 4. Comparison of characteristics between women delivered ≥ 34 and <34 weeks' gestation (N=90).

Characteristics	Delivery at <34 weeks N=24	Delivery at ≥ 34weeks N=66	P value
	Mean ± SD	Mean ± SD	
Age (years)	31.5 ± 5.8	31.9 ± 4.4	0.769
Gestational age at cerclage (weeks)	18.6 ± 4.2	17.7 ± 4.4	0.422
Cervical length (mm) (N=70)	18.0 ± 14.9(N=17)	28.2 ± 10.5(N=53)	0.002
	N (%)	N (%)	
Cervical dilatation			0.046
No dilatation	14 (58.3%)	55 (83.3%)	
1-2 cm	7 (29.2%)	8 (12.1%)	
>3 cm	3 (12.5%)	3 (4.5%)	
Bulging of membranes	8 (33.3%)	5 (7.6%)	0.002
Type of cervical cerclage			0.001
Prophylactic	14 (58.3%)	59 (89.4%)	
Rescue	10 (41.7%)	7 (10.6%)	
Progesterone treatment	9 (37.5%)	36 (54.5%)	0.153
Antibiotic prophylaxis	21 (87.5%)	61 (92.4%)	0.435
Maternal complications	11 (45.8%)	6 (9.1%)	<0.001
Uterine contraction	6 (25%)	5 (7.6%)	
Vaginal bleeding	1 (4.2%)	1 (1.5%)	
Rupture of membrane	2 (8.3%)	0	
Others*	2 (8.3%)	0	

*Others: cervical tear, chorioamnionitis

cerclage in a patient who had 7 cm. of cervical dilatation and bulging of membranes, and delivered at 33 weeks and 4 days of gestation with good neonatal outcomes.[14] The success rate of the prophylactic group was higher than the rescue group, similar to previous studies (78% vs 53%).[18,19] For clinical applications, The success rate can apply to counsel the pregnant women who has cervical incompetence and plan to do the cervical cerclage. Early identification of women at risk of cervical incompetence and early treatment will improve outcomes.

A strength of the present study is that almost all of the cervical cerclage procedures were performed by a single experienced obstetrician, meaning that there was no variation in the surgeon skill or technique.

Nonetheless, this study has a number of limitations. The recommendations for cervical cerclage was changed after receiving new research data.[4,20] History indicated that cervical cerclage had changed from three or more second trimester pregnancy losses to only one or more previous second trimester pregnancy losses. The data used in this study used the previous criteria to diagnose cervical incompetence in some cases, meaning that some cases of cervical incompetence may have been missed. At present, transvaginal ultrasounds are available in all hospitals. Nowaday, we uses cervical length to co-evaluate with any history of prior preterm births. Recent meta-analysis[21] shows that cervical cerclage in patients with a history of prior preterm births and short cervical length

(<25 mm.) is effective at reducing preterm births, and also avoids unnecessary cervical cerclage based solely on history. In this study, charts from the past 10 years were reviewed, but some cases provided no information about cervical length. Future additional research and RCTs are therefore still require.

CONCLUSION

The success rate of cervical cerclage procedures in the 10 year period at Siriraj Hospital was 73.3%. The success rate in the prophylactic group was 80.8%, while it was 41.2% in the rescue cervical cerclage procedure group. Possible associated factors included cervical length, cervical dilatation, bulging of membranes, and prophylactic procedure.

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The Vertical Ground Reaction Force and Temporal-Spatial Parameters of Transfemoral Amputees Wearing Three Prosthetic Knee Joints Available in Thailand: a Pilot Study

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ABSTRACT

Objective: To examine the temporal-spatial characteristics of transfemoral amputees using three prosthetic knees available in Thailand. In addition, the estimated vertical Ground Reaction Force (vGRF) was explored, in particular the graphical differences in the M-shape of the vGRF pattern amongst each of the knees and the sound limb.

Methods: Three transfemoral amputees were fitted with three different prosthetic knee joints (Chulalongkorn University (CU) Polycentric Knee Joint, Prosthesis Foundation Knee, Otto Bock 3R20) and performed walking trials while the vGRF and temporal-spatial parameters were collected for all participants.

Results: Similarities existed amongst GRF metrics across all prosthetic knees. Stance and swing time in the CU Polycentric Knee Joint was similar to that of the sound limb. Walking speeds were highest in the Otto Bock 3R20 and lowest in the Prosthesis Foundation Knee.

Conclusion: This preliminary pilot testing revealed similarities amongst all three prosthetic knees. Future research with more participants and additional analysis could further elucidate characteristics of these prosthetic knees.

Keywords: Prosthetic knee joint; transfemoral amputee gait; vertical ground reaction, temporal-spatial parameters
(Siriraj Med J 2019; 71: 399-404)

INTRODUCTION

Lower extremity amputations are occurring at an increasing rate in South East Asia.[1] The provision of functional lower limb prosthesis is common place throughout the world and the advancement of technologies has led to an improved quality of life for persons afflicted with transfemoral amputations.[2,3] Still, for the transfemoral amputee, the loss of the anatomical knee joint presents a plethora of problems.[4] The biggest being the inability to provide anatomical flexion and extension of the prosthesis. The able-bodied person has an intact knee joint and therefore a greater control over placement of the foot during walking. The above knee amputee has increased metabolic cost and a disturbed sensory control because of the absence of normal joint and muscular functions. They must make muscle adaptions in their non-affected limb musculature to compensate for these residual limb issues.[5] Furthermore, there are lowered joint torques and

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mechanical energy requirements for the transfemoral prosthesis limb and an increased demand placed on the sound limb compared to able-bodied persons.[6] Fortunately, efforts have been made to reduce the inherent reduced swing phase duration that occurs with the prosthetic knee joint, through either mechanical or hydraulic knees.[7]

The prosthetist creating a transfemoral prosthesis has a number of suitable prosthetic knee options available to them. The single axis hinged knee joints that were commonly prescribed several decades ago are no longer a standard of care for the ambulating amputee. Modern knee joints have integrated hydraulic mechanisms for added functionality.[19] Prosthetic knees which take into consideration direction of the instantaneous center of rotation (ICR) while attempting to mimic the sliding motion of the anatomical knee joint, are more commonly provided to users.[8] A commonly used knee in Thailand is the Otto Bock 3R20 (Otto Bock, Duderstadt, Germany), which is a 4-bar linkage knee joint with a mechanical swing phase control. The kinematics of transfemoral amputees walking in this knee have been explored before.[9] The 3R20 knee has been shown to allow for decreased mean values of stride length and increased walking speed than its lower end model the 3R15.[10,11]

However, there has been an increased push by the United Nations for affordable locally developed rehabilitation technologies over recent years.[12] Thailand has answered the call by developing its own prosthetic knee joints. The CU Polycentric Knee Joint and the Prosthesis Foundation Knee were both designed and developed with a desire to provide locally made prosthetic technology to Thai amputees. The CU Polycentric Knee Joint is designed to closely mimic the motion of the anatomical knee joint through utilization of a unique sliding apparatus and the Prosthesis Foundation Knee is a 4-bar linkage polycentric knee joint. There is a dearth of objective data and scholarship for both of these knee joints as they are still relatively new to the market. Of unique interest to researchers and prosthetists are the performance features provided by each of the aforementioned knee joints.

Objectively measuring knee characteristics and stability can be performed through use of instrumented motion analysis exploring kinematic and kinetic parameters, although this procedure requires the use of resource demanding laboratory equipment and training. Exploring stability through alternative means such as plantar pressure distribution analysis is another viable option.[20] Pressure mat systems are useful for measuring pressure patterns occurring under the foot and to help understand temporal-spatial parameters such as stance and swing variability and cadence. By combining the calculated simultaneous estimations of vertical ground reaction force (vGRF) and center of pressure (COP), the pressure mat system becomes a useful tool for identifying features of the aforementioned prosthetic knee joints.[13] The objective of this study was to examine the temporal-spatial characteristics of transfemoral amputees using three prosthetic knees available in Thailand. In addition, the estimated vGRF was explored, and in particular the graphical differences in the M-shape of the vGRF pattern amongst each of the knees and the sound limb.

MATERIALS AND METHODS

This study protocol was approved by Siriraj Institutional review Board (Si 013/2014).

Participants

All participants provided written informed consent prior to completing the Siriraj Hospital Faculty of Medicine Mahidol University SIRB protocol. Inclusion criteria were restricted to unilateral transfemoral amputees and patients of the Prosthetic and Orthotic clinic at Siriraj Hospital. Three eligible participants were recruited in this study. Each participant was 2-years post amputation, had a medium stump length, at least a grade 4 out of 5 on the manual muscle test (MMT) as determined by the study prosthetist. Participants' were previously familiar with walking with their transfemoral prostheses for at least one year. An Amputee Mobility Predictor (AMPro) activity level of either 3 or 4 (MFCL K Level) was required for all participants.[14]

Prosthesis

Each participant performed walking trials in a newly provided prosthesis which received the Otto Bock 3R20, CU Polycentric Knee Joint or Prosthesis Foundation Knee (Fig 1). For the entirety of the study, all participants received a quadrilateral socket design with passive suction suspension and were then randomly assigned to receive either of the study knees, a solid-ankle cushion heel (SACH) foot which was appropriate for persons requiring stability and comfort during walking, and a 1 cm heel height shoe. Participants performed an hour walking accommodation period at their preferred walking speed along an indoor walkway prior to all data collection. Furthermore, each of the prosthesis was properly aligned by the study prosthetist according to manufacturer guidelines.

Walking trials

All participants performed outcome measures in their prosthesis under each prosthetic knee configuration for



Fig 1. Image of three prosthetic knees tested: From left to right; Chulalongkorn University (CU) Polycentric Knee Joint, Prosthesis Foundation Knee, Otto Bock 3R20

a total of three trials. The Zebris Gait Mat System (zebris Medical GmbH, Germany) and FDM Software were used to collect and analyze temporal-spatial parameters as well as vGRF. Participants were instructed to walk along the designated walkway at their preferred walking speed.

Data analysis

Data analysis from the Zebris Gait Mat System was performed using Microsoft Excel Analysis Toolpak (Microsoft, US). Key parameters of interest were walking velocity, percentages of stance and swing phases of both limbs, and step length. Moreover, with respects to vGRF, the visible differences between the sound side and prosthesis side first peak (weight acceptance), second peak (push-off) and valley of vGRF were analyzed. The GRF data was reported in Newton's (N) and was normalized to body weight with each step time being normalized to 100% of the gait cycle, where a complete cycle was defined as two consecutive heel contacts on a single foot.

RESULTS

Participant demographics and activity classification are provided in Table 1. Slight differences were observed for comparisons of the first peak and valley of the mean GRF for each of the study knees and sound limb (Fig 2). Similarities existed amongst GRF metrics across all prosthetic knees. Furthermore, across all prosthetic knees, the stance phase was shorter on the prosthetic side than on the sound side. When prosthetic and sound sides were compared, the curves were mostly dissimilar along the second peak and valley. The valley of vGRF of the sound limb were lowest and highest when participants wore the Prosthesis Foundation Knee (Fig 3). Stance and swing phase differences amongst prosthetic knees and the sound limb showed that the CU Polycentric Knee Joint exhibited stance (57%) and swing (43%) times closer to the sound limb (70%) and (30%) respectively (Figs 4 and 5). The preferred walking velocities showed a higher velocity when participants used the 3R20, and lowest velocity when using the Prosthesis Foundation Knee (Table 2). With respects to spatial parameters, the step lengths of participants using the CU Polycentric Knee Joint (68.33 cm) and Prosthesis Foundation Knee (68.33 cm) were closer in length to the sound side limb (51.88 cm), whereas the longest step length was observed when participants wore the 3R20 (72.33 cm).

TABLE 1. Demographic data and MCFL classification for three study participants.

Participant	Amputation Cause	K-Level	Age	Height (kg)	Weight (cm)	BMI
Participant 1	Traumatic	3	17	168	52	18.42
Participant 2	Traumatic	3	46	173	68	22.72
Participant 3	Traumatic	3	53	164	55	20.44

*MCFL; Medicare Functional Classification Level, K-Level; MCFL, BMI = kg/m^2

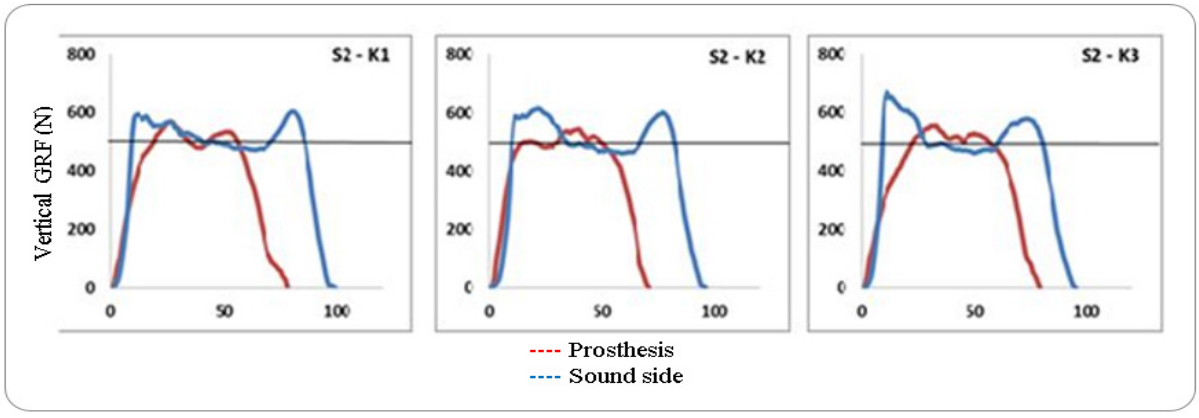


Fig 2. Example of one participant's vGRF curve comparisons of vertical ground reaction force for three prosthetic knees and sound side limb. (k1:CU Polycentric Knee Joint, k2:Prosthesis Foundation Knee, k3:Otto Bock 3R20)

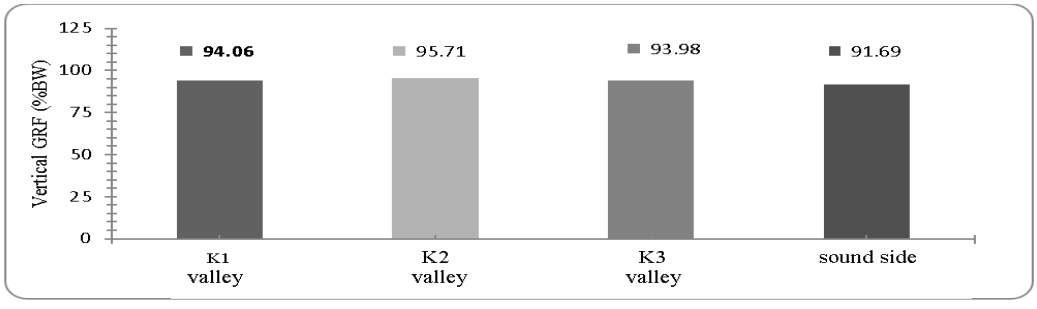


Fig 3. Comparisons of vertical ground reaction force of three prosthetic knees and sound side limb at TVF (valley of the force in the vertical direction). Bars represent average vGRF for %BW (k1: CU Polycentric Knee Joint, k2: Prosthesis Foundation Knee, k3: Otto Bock 3R20)

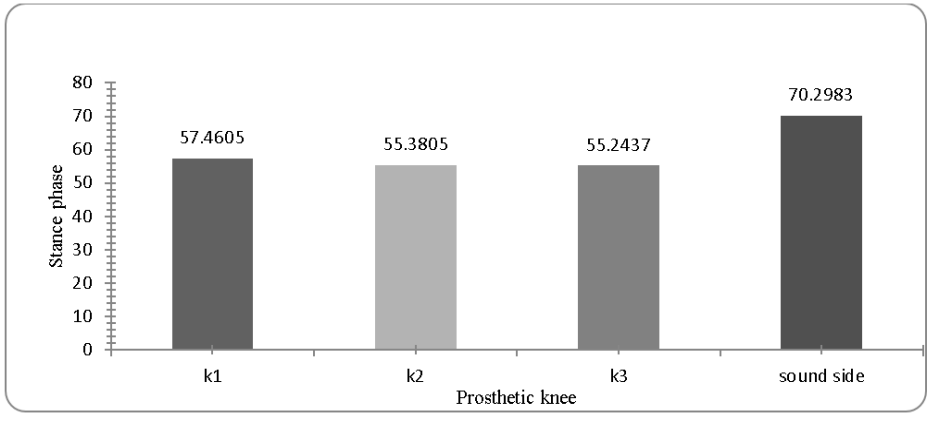


Fig 4. Mean stance phase duration times for three prosthetic knees and sound side during a walking trial (k1: CU Polycentric Knee Joint, k2: Prosthesis Foundation Knee, k3: Otto Bock 3R20).

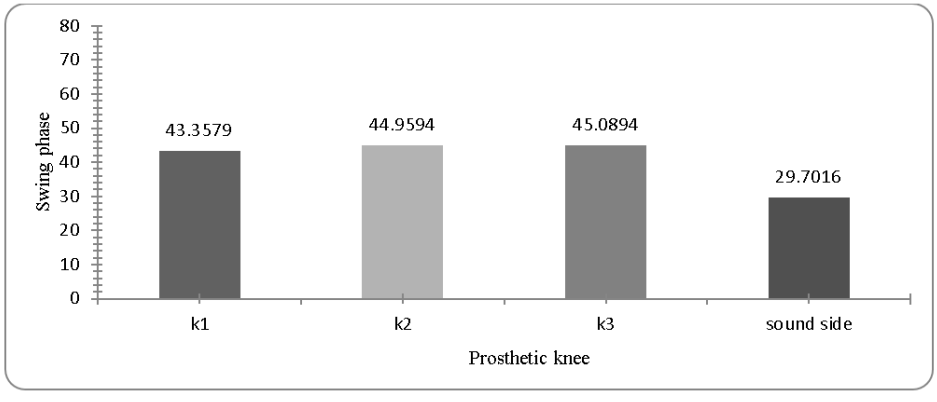


Fig 5. Mean swing phase duration times for three prosthetic knees and sound side during a walking trial (k1: CU Polycentric Knee Joint, k2: Prosthesis Foundation Knee, k3: Otto Bock 3R20).

TABLE 2. Temporal-spatial parameters for three prosthetic knees.

Prosthetic knee	Velocity (m/s)	Step length (cm)
CU Polycentric Knee Joint	0.814	68.33
Prosthesis Foundation Knee	0.792	68.33
Otto Bock 3R20	0.892	72.33
Sound Limb	N/A	51.88

DISCUSSION

The purpose of this pilot study was to explore GRF and temporal-spatial characteristics of three prosthetic knees available to the Thai transfemoral amputee. Overall, the investigation revealed small differences in valley vGRF curve magnitudes between prosthetic knees and the sound limb. The CU Polycentric Knee Joint was capable of stance and swing times that were closer to that of the sound limb and increased preferred walking speed was seen in participants wearing the 3R20. Able bodied gait is characterized by roughly 60% of gait spent in stance and 40% of time spent in swing.[18] Previous investigations have observed the mechanical swing phase control 3R20 to be favorable by users because of a greater sense of stability over a pneumatic swing phase control knee.[21]

The CU Polycentric Knee Joint's ability to provide a more identical swing and stance time is an interesting finding which might be as a result of its lowered Instant Centre of Rotation (ICR) than the two 4-bar linkage knees. The CU Polycentric Knee Joint and Prosthesis Foundation Knee had step lengths that more closely resembled sound limb step lengths. The increased walking speed and larger step length seen in the 3R20 might be a result of a decreased dependence on compensatory mechanisms of the participants,[15] although our data does not allow us to determine that entirely. The lower limb amputee lowers walking speed to reduce the Rate of Metabolic Energy Expenditure (RMEE) (Vo2, mL/kg per min).[16,17] Walking speed and RMEE could be explored to determine the relationship between speed of walking and metabolic cost when fitted with these knees.

This preliminary investigation was not without its limitations. The small participant sample of three transfemoral prosthesis users makes generalizing the results of this study difficult. Our decision to analyze data from three trials might have resulted in variance in amputee walking performance. Although we noticed no marked differences amongst trial metrics, an increase in walking trials over several days could reveal the chance of trial-to-trial and day-to-day differences. Future investigations which recruit a larger sample size and able bodied matched control group should be pursued. Also these knee joints should be compared with others commonly used in prosthetic practice. We used a pressure measurement system, which is capable of quantifying center of pressure, but unable to directly measure a force vector applied. Other investigations have utilized coefficients collected from calibration trials to delineate gait phase and in doing so correct GRF and COP data collected from pressure mats. This in turn allows for a better estimation of forces in each foot during the double limb support period.[13] This study focused on vGRF and temporal-spatial parameters, so a more robust description of walking with these knees including kinematic, electromyography and energy consumption should be conducted. There are a number of additional GRF measurements that were not explored in this current study that should be in future work, such as weight acceptance and push-off as well as impulses and joint kinematics as well.[18] Ultimately, the lower limb prosthesis user, especially those living in resource limited environments, will be required to walk and traverse in a variety of terrain. Therefore, research exploring the performances of amputees using these and other new prosthetic technologies during free-living activity should be explored.

CONCLUSION

This study presents a preliminary investigation on the gait characteristics of transfemoral prosthesis wearers using three prosthetic knees available to the Thai amputee. Special importance was given to the parameters that indicate walking ability. The CU Polycentric Knee Joint should be recognized for its ability to promote a more symmetrical gait and the 3R20, for its potential to increase walking speeds.

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Utility of the Siriraj Psoriatic Arthritis Screening Tool, the Thai Psoriasis Epidemiology Screening Tool, and the Early Arthritis for Psoriatic Patients Questionnaire to Screen for Psoriatic Arthritis in an Outpatient Dermatology Clinic Setting, and Identification of Factors Significantly Associated with Psoriatic Arthritis

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ABSTRACT

Objective: To assess the clinical utility of the Psoriasis Epidemiology Screening Tool (PEST), the Early Arthritis for Psoriatic Patients (EARP) questionnaire, and the Siriraj Psoriatic Arthritis Screening Tool (SiPAT) as screening tools for psoriatic arthritis (PsA), and to identify factors significantly associated with PsA.

Methods: This cross-sectional study included adult psoriasis patients who attended the outpatient clinic at Siriraj Hospital and had not been diagnosed with PsA during 1 March 2017 to 28 February 2018. Participants completed the EARP, PEST, and SiPAT, after which musculoskeletal history was taken, and examination and radiography were performed. Diagnosis of PsA was based on Classification Criteria for Psoriatic Arthritis. Receiver operator characteristic (ROC) curves, sensitivity, and specificity were used to determine assessment tool performance. Logistic regression analysis was used to identify factors associated with PsA.

Results: Eighty-seven patients with a mean age of 45.90±14.75 years were enrolled. Twenty-six (29.88%) patients were diagnosed as PsA. According to ROC values, EARP had the best discriminative power (0.83) for distinguishing between psoriatic patients with and without PsA (SiPAT: 0.78, PEST: 0.77). SiPAT had the highest sensitivity (92.3%), followed by EARP (84.6%) and PEST (50.0%); whereas, PEST had the highest specificity (82.0%), followed by EARP (62.3%) and SiPAT (54.1%) for detecting PsA. Multivariate analysis revealed body surface area involvement >10% to be the only independent predictor of PsA (OR: 2.99, 95% CI: 1.09-8.21).

Conclusion: SiPAT is an effective and simple to use tool for screening PsA in psoriasis patients. Body surface area involvement >10% is a significant predictor of PsA.

Keywords: Factors associated with PsA; Psoriasis Epidemiology Screening Tool (PEST); screening tools for psoriatic arthritis; the Early Arthritis for Psoriatic Patients (EARP) questionnaire; the Siriraj Psoriatic Arthritis Screening Tool (SiPAT) (Siriraj Med J 2019; 71: 405-413)

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INTRODUCTION

Psoriatic arthritis (PsA) is a multidimensional musculoskeletal inflammatory disease that is associated with psoriasis (Ps). The prevalence of PsA in Ps was reported to range from 6 to 42%.[1] Early detection and intervention is important for good long-term outcome in terms of achieving remission, stopping and reversing structural change, and regaining and preserving function.[2] Most patients present with Ps before developing PsA.[1] Thus, dermatologists and general practitioners play an important role in the identification of PsA. However, up to 40% of patients with Ps had undiagnosed PsA.[3] A simple and effective PsA screening tool is, therefore, needed. Currently available screening tools include the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire[4], the Psoriasis Epidemiology Screening Tool (PEST)[5], and the Early Arthritis for Psoriatic Patients (EARP) questionnaire[6] for patients with Ps, and the Toronto Psoriatic Arthritis Screen II (ToPAS II) questionnaire[7] for both Ps patients and the general population. The reported variation in the performance of these tools may be due to patient musculoskeletal manifestations.[8-9] PsA-related musculoskeletal manifestations are divided into the following 3 groups: spinal inflammation, peripheral arthritis, and enthesitis. The Siriraj Psoriatic Arthritis Screening Tool (SiPAT), which focuses on the evaluation of musculoskeletal manifestations, is a composite tool that was developed via the adoption of 2 questions from the EARP questionnaire, and 1 question from PEST.[10] The copyright owners of the PEST and EARP tools granted formal permission for these assessments to be translated into Thai language and validated.[10] A previous study showed the sensitivity and specificity to be 91% and 69% for SiPAT; 83% and 79% for EARP; and, 72% and 90% for PEST, respectively (all Thai versions).[10] However, there are two notable reasons why the aforementioned sensitivities may have been overestimated. First, that study included both diagnosed and undiagnosed PsA patients. Second, it was performed in a psoriasis clinic where the majority of patients would have severe skin disease and/or musculoskeletal symptoms. Accordingly, the aim of this study was to investigate the clinical utility of the SiPAT, the PEST, and the EARP questionnaire to screen for PsA in an outpatient dermatology clinic setting, and to identify factors significantly associated with PsA.

MATERIALS AND METHODS

Adult psoriasis patients aged 18 years or older who attended the outpatient dermatology clinic, Siriraj Hospital during 1 March 2017 to 28 February 2018, and that had never been diagnosed with PsA were asked to voluntarily participate in this cross-sectional study. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 659/2012), and written informed consent was obtained from all participants. This study complied with the principles set forth in the 1964 Declaration of Helsinki and all of its subsequent amendments.

All enrolled patients were asked to individually complete (i) the validated Thai version of PEST, (ii) the validated Thai version of EARP, and (iii) the SiPAT.[10] These three questionnaires were provided not only as three separate forms, but they were also given in random order to avoid completion bias. Table 1 shows all of the questions contained in the three questionnaires. The EARP and PEST contain 10 and 5 questions, respectively, with a score of 1 for each positive answer and a score of 0 for each negative answer. A score of 3 or higher for each of these two questionnaires was considered to indicate that the patient was positive for PsA. The SiPAT consists of 3 questions designed to elicit information about the presence of inflammatory back pain, peripheral arthritis, and heel enthesitis. A positive answer was scored as 1, and a negative answer was scored as 0. A SiPAT score of 1 or higher was considered to indicate that the patient was positive for PsA.

An evaluation of patient medical records and physical examinations were then performed. Current non-steroidal anti-inflammatory drugs (NSAIDs) use was defined as current use or drug discontinuation for less than 2 weeks before recruitment. Musculoskeletal examination was performed independently by one expert rheumatologist (PC). Rheumatoid factor (RF), and radiography of the cervical spine, lumbar spine, pelvis, hands, and feet were performed. All radiography results were interpreted by one expert rheumatologist (PC). The expert rheumatologist (PC) who examined patients and evaluated patient data was blinded to patient questionnaire data from the EARP, PEST, and SiPAT. PsA was diagnosed by a rheumatologist according to the Classification Criteria for Psoriatic Arthritis (CASPAR).[11] Patterns of PsA, including peripheral arthritis, axial inflammation, and enthesitis, were defined using patient history, physical examination of joint/musculoskeletal pain, and radiography.

Sample size calculation and statistical analysis

Using an estimated specificity of about 60% and

TABLE 1. The questions asked on the Early Arthritis for Psoriatic Patients (EARP) questionnaire, the Psoriasis Epidemiology Screening Tool (PEST) questionnaire, and the Siriraj Psoriatic Arthritis Screening Tool (SiPAT). A 'yes' answer receives a score of 1, and a 'no' answer receives a score of 0.

Assessment tools	Yes	No
EARP*		
1. Do your joints hurt?	1	0
2. Have you taken anti-inflammatory drugs more than twice a week for joint pain within the last 3 months?	1	0
3. Do you wake up at night because of low back pain?	1	0
4. Do you feel stiffness in your hands for more than 30 minutes in the morning?	1	0
5. Do your wrists and fingers hurt?	1	0
6. Do your wrists and fingers swell?	1	0
7. Does one finger hurt and swell for more than 3 days?	1	0
8. Does your Achilles tendon swell?	1	0
9. Do your feet or ankles hurt?	1	0
10. Do your elbows or hips hurt?	1	0
PEST**		
1. Have you ever had a swollen joint (or joints)?	1	0
2. Has a doctor ever told you that you have arthritis?	1	0
3. Do your fingernails or toenails have holes or pits?	1	0
4. Have you had pain in your heel?	1	0
5. Have you had a finger or toe that was completely swollen and painful for no apparent reason	1	0
SiPAT***		
1. Do you wake up at night because of low back pain?	1	0
2. Do your wrists and fingers swell?	1	0
3. Have you had pain in your heel?	1	0

*,**Formal permission to validate and translate these two assessment tools into Thai language was obtained from the copyright owners. The validated Thai versions of these two questionnaires were used in this study. ***Items contained in the SiPAT questionnaire were adopted from items 3 and 6 of the EARP, and from item 4 of the PEST. Its validated version was used in this study.

a 95% confidence interval (CI) of 60% ± 12% from previous study, a sample size of 65 subjects without PsA was required for this study.[10] Based on an estimated prevalence of PsA of about 25%, a total of 88 subjects with Ps was calculated.

Descriptive statistics were used to summarize patient demographic and clinical data. Pearson's Chi-square test or Fisher's exact test was used to compare categorical data. Independent t-test and Mann-Whitney U test were used to compare continuous parametric and continuous non-parametric data, respectively. Receiver operating characteristic (ROC) curves were generated and analyzed to evaluate the diagnostic performance of the EARP, PEST, and SiPAT questionnaires. The area under the ROC curve (AUC) measured how well each questionnaire could distinguish between psoriatic patients with and without PsA. An AUC of 0.5 indicated no distinguishable difference between the two conditions, while an AUC of 1 reflected a clear and absolute distinguishable difference between PsA and no PsA.[12] Logistic regression was employed to identify factors significantly associated with PsA. Variables with a *p*-value less than or equal to 0.2 in univariate analysis were entered into multivariate analysis to identify independent predictors of PsA. A *p*-value less than or equal to 0.05 in multivariate analysis was regarded as being statistically significant. Data were analyzed using PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Eighty-eight participants were initially enrolled; however, one participant was excluded before any investigations were performed due to age less than 18 years. Eighty-seven patients with a mean age of 45.90±14.75 years were enrolled in this study. The most common underlying diseases were hypertension (30%), dyslipidemia (27.6%), and diabetes mellitus (13.8%). Primary, secondary, vocational, and tertiary education was completed in 16, 21, 9, and 41 patients, respectively. All patients were able to answer all of the questions on all three questionnaires (18 questions in total) within 5 minutes. According to CASPAR criteria, 26 (29.9%) patients had newly established PsA. Of patients with no PsA, 34 (55.7%) patients had other musculoskeletal diseases, including mechanical back pain (14 patients), knee osteoarthritis (10 patients), hand osteoarthritis (5 patients), heel pain related to activity (4 patients), and gout (1 patient). Six (23.1%) patients with PsA also had other musculoskeletal diseases, including mechanical back pain (4 patients), knee osteoarthritis (1 patient), and coexisting mechanical back pain and knee osteoarthritis (1 patient). The data in Table 2 shows longer disease duration, presence of psoriatic nail, and body surface area (BSA) involvement >10% to be significantly more common in patients with PsA. Moreover, the EARP, PEST, and SiPAT scores obtained from psoriatic patients with PsA were significantly higher than the scores obtained from psoriatic patients without PsA.

The diagnostic performance of the three questionnaires for detecting PsA and patterns of PsA is shown in Table 3. According to area under the ROC curve (AUC) values, the EARP questionnaire demonstrated the best discriminative power (0.83) for distinguishing between psoriatic patients with and without PsA (SiPAT: PEST: 0.77). All three questionnaires performed well in all patterns of PsA, except in purely axial inflammation. The SiPAT had the highest sensitivity (92.3%), followed by EARP (84.6%) and PEST (50.0%). Conversely, the PEST had the highest specificity (82.0%), followed by EARP (62.3%) and SiPAT (54.1%), regardless of musculoskeletal patterns. For subgroup of PsA pattern analysis, the sensitivity of EARP and SiPAT were still good in the three major musculoskeletal patterns regardless of combinations of other patterns, except pure axial inflammation. Conversely, the sensitivity of PEST were lower than EARP and SiPAT in the three major musculoskeletal patterns regardless of combinations of other patterns, especially axial pattern. In addition, the PEST could not detect any PsA patients with pure axial inflammation.

Univariate analysis showed disease duration more than 10 years [odds ratio (OR): 3.03, 95% CI: 1.14-8.03; p=0.026], nail involvement (OR: 5.02, 95% CI: 1.07-23.52; p=0.040), and BSA involvement higher than 10% (OR: 3.58, 95% CI: 1.36-9.41; p=0.010) to be significantly associated with PsA (Table 4). Multivariate analysis revealed BSA involvement >10% to be the only independent predictor of PsA (OR: 2.99, 95% CI: 1.09-8.21; p=0.034) (Table 5).

DISCUSSION

Dermatologists need an effective and simple to use screening tool that can differentiate between Ps patients with and without PsA. Several of the available PsA screening tools, including PASE (15 questions), EARP (10 questions), and ToPAS II (13 questions with pictures), contain at least 10 questions, which may be complicated, and time-consuming for use in a dermatology outpatient clinic setting.[4, 6-7] The Psoriatic arthritis UnclutteRed screening Evaluation-4 (PURE-4) (4 questions) was recently developed for dermatologists to screen for PsA.[13] The overall performance of PURE-4 for diagnosing newly established PsA was good with sensitivity (85.7%) and specificity (83.6%), and an AUC of 0.88.[13] The Simple Psoriatic Arthritis Screening (SiPAS) questionnaire (5 questions), which is another tool that was developed to screen for PsA, was reported to have a sensitivity of 79% and a specificity of 87%.[14]

SiPAT was designed as a short PsA screening tool (3 questions), which is similar to the 4-question PURE-4 and the 5-question SiPAS. The three questions from the PEST and EARP assessments that were considered most relevant to detecting the 3 major patterns of PsA were adopted for use in the SiPAT questionnaire.[10] Regardless of musculoskeletal patterns, the specificity of SiPAT was much lower than that of the PURE-4 and the SiPAS for detecting PsA. The study population in a study that investigated the performance of the SiPAS did not include patients with other rheumatic diseases that can mimic PsA.[14] In contrast, our study included all Ps patients, which included a high proportion of other musculoskeletal diseases, especially mechanical back pain. Seven patients without PsA answered 'yes' for the first question of the SiPAT (*Do you wake up at night because of low back pain?*). Of those 7 patients, six had mechanical back pain, and the one remaining patient had no evidence of musculoskeletal disease. Low back pain is a common symptom in general population. To improve the performance of the SiPAT questionnaire for detecting spinal inflammation, the question used to detect inflammatory back pain should be amended in the future.

TABLE 2. Demographic and clinical characteristics compared between patients with and without psoriatic arthritis (PsA) (N=87).

Characteristics	No PsA (n=61)	PsA (n=26)	*P*-value
Age (yrs), mean±SD	46.0±14.7	45.6±15.3	0.896
Male gender, n (%)	30 (49.2%)	16 (61.5%)	0.290
Age of onset (yrs), n (%)			0.784
<40	38 (62.3%)	17 (65.4%)	
≥40	23 (37.7%)	9 (34.6%)	
Disease duration (yrs), median (IQR, min-max)	7.6 (10.8, 0.6-43.6)	12.2 (14.4, 0.26-40.5)	*0.018*
Psoriatic nail, n (%)	43 (70.5%)	24 (92.3%)	*0.027*
Body mass index ≥25 kg/m^2, n (%)	31 (53.4%)	17 (68.0%)	0.218
Body surface area (BSA) involvement, n (%)			
≤10%	46 (75.4%)	12 (46.2%)	*0.008*
>10%	15 (24.6%)	14 (53.8%)	
PASI, n (%)			
≤10%	49 (80.3%)	18 (69.2%)	0.260
>10%	12 (19.7%)	8 (30.8%)	
Past and current treatment, n (%)			
Only topical treatment	23 (37.7%)	9 (34.6%)	0.784
Systemic treatment + phototherapy	38 (62.3%)	17 (65.4%)	
Methotrexate use for psoriasis, n (%)			
Current	18 (29.5%)	7 (26.9%)	0.807
NSAIDs use, n (%)			
Current	2 (3.3%)	4 (15.4%)	0.063
Past	19 (31.1%)	6 (23.1%)	0.446
Positive rheumatoid factor (RF), n (%)	17/58 (29.3%)	9/25 (36.0%)	0.547
Pattern of PsA*, n (%)			
Peripheral arthritis	-	17 (65.4%)	
Axial inflammation	-	15 (57.7%)	
Enthesitis	-	8 (30.8%)	
Assessment tools, mean±SD			
EARP score	1.9±2.0	4.5±1.9	*<0.001*
PEST score	1.4±1.2	2.7±1.3	*<0.001*
SiPAT score	0.6±0.7	1.5±0.8	*<0.001*

A *p*-value<0.05 indicates statistical significance

Abbreviations: SD = standard deviation; IQR = interquartile range; PASI = Psoriasis Area & Severity Index; NSAIDS = non-steroidal anti-inflammatory drugs; EARP = Early Arthritis for Psoriatic Patients questionnaire; PEST = Psoriasis Epidemiology Screening Tool; SiPAT = Siriraj Psoriatic Arthritis Screening Tool

*One patient could have one more pattern of PsA

TABLE 3. Diagnostic performance of the Early Arthritis for Psoriatic Patients (EARP) questionnaire, the Psoriasis Epidemiology Screening Tool (PEST), and the Siriraj Psoriatic Arthritis Screening Tool (SiPAT).

Tools	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
All psoriatic arthritis patients (n=26)							
EARP	0.83 (0.73-0.92)	84.6%	62.3%	48.9%	90.5%	2.24	0.24
PEST	0.77 (0.67-0.87)	50.0%	82.0%	54.2%	79.4%	2.78	0.61
SiPAT	0.79 (0.69-0.89)	92.3%	54.1%	46.2%	94.3%	2	0.15
Patients with predominant peripheral arthritis (n=17)							
EARP	0.92 (0.86-0.98)	100%	62.3%	42.5%	100%	2.65	0
PEST	0.85 (0.75-0.95)	70.6%	82.0%	52.2%	90.9%	3.92	0.36
SiPAT	0.83 (0.74-0.93)	100%	54.1%	37.8%	100%	2.17	0
Patients with predominant axial inflammation (n=15)							
EARP	0.75 (0.62-0.89)	73.3%	62.3%	32.4%	90.4%	1.94	0.43
PEST	0.70 (0.57-0.83)	33.3%	82.0%	31.3%	83.3%	1.85	0.81
SiPAT	0.75 (0.62-0.89)	86.7%	54.1%	31.7%	94.3%	1.89	0.25
Patients with predominant enthesitis (n=8)							
EARP	0.87 (0.74-1.00)	87.5%	62.3%	23.3%	97.4%	2.32	0.20
PEST	0.83 (0.69-0.97)	62.5%	82.0%	31.3%	94.3%	3.47	0.46
SiPAT	0.86 (0.75-0.97)	100%	54.1%	22.2%	100%	2.18	0
Patients with pure peripheral arthritis (n=9)							
EARP	0.92 (0.86-0.99)	100%	61.3%	27.3%	100%	2.58	0
PEST	0.84 (0.71-0.96)	66.7%	82.3%	35.3%	94.4%	3.77	0.40
SiPAT	0.81 (0.69-0.93)	100%	51.6%	23.1%	100%	2.07	0
Patients with pure axial inflammation (n=5)							
EARP	0.54 (0.34-0.74)	40.0%	62.3%	8.0%	92.7%	1.06	0.96
PEST	0.56 (0.39-0.73)	0.0%	82.0%	0.0%	90.1%	0	1.22
SiPAT	0.58 (0.31-0.84)	60.0%	54.1%	9.7%	94.3%	1.31	0.74

Patients without PsA (n=61) were included in all subsections of this analysis. There was no patient with pure enthesitis, so it was not further analyzed.

Abbreviations: AUC = area under the curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.

TABLE 4. Univariate analysis for factors associated with psoriatic arthritis (PsA).

Factors	Patients (%)		Odds ratio (95% CI)	*P*-value
	No PsA	PsA		
Sex				
Male	30 (49.2)	16 (61.5)	1.65 (0.65 - 4.22)	0.292
Female	31 (50.8)	10 (29.9)	1	
Obesity, BMI (kg/m^2)				
≥ 25	31 (53.4)	17 (68.0)	1.85 (0.69 - 4.96)	0.221
< 25	27 (46.6)	8 (32.0)	1	
Disease duration (years)				
≥ 10	26 (42.6)	18 (69.2)	3.03 (1.14 - 8.03)	0.026
< 10	35 (57.4)	8 (30.8)	1	
Nail involvement				
Yes	43 (70.5)	24 (92.3)	5.02 (1.07 - 23.52)	0.040
No	18 (29.5)	2 (7.7)	1	
Body surface area (BSA)				
> 10%	15 (24.6)	14 (53.8)	3.58 (1.36 - 9.41)	0.010
≤ 10%	46 (75.4)	12 (46.2)	1	
Psoriasis Area and Severity Index (PASI)				
> 10%	12 (19.7)	8 (30.8)	1.82 (0.638 - 5.16)	0.264
≤ 10%	49 (80.3)	18 (69.2)	1	
Current treatment				
Topical treatment	29 (47.5)	12 (46.2)	1.06 (0.42 - 2.65)	0.906
Systemic treatment + phototherapy	32 (52.5)	14 (53.8)	1	

Abbreviations: CI = confidence interval, BMI = body mass index

TABLE 5. Multivariate analysis for factors associated with psoriatic arthritis.

Variable	Adjusted odds ratio (95%CI)	*P*-value
Disease duration > 10 years	2.63 (0.94-7.37)	0.065
Nail involvement	4.31 (0.87-21.42)	0.075
BSA involvement > 10%	2.99 (1.09-8.21)	0.034

Abbreviations: CI = confidence interval, BSA = Body surface area

Conversely, the sensitivities of the SiPAT were very high, with 90-100% sensitivity for predominant enthesitis and peripheral arthritis in both previous study[10] and the current study. However, no sensitivities and specificities for specific musculoskeletal manifestations were reported for the PURE-4 or the SiPAS. Moreover, they have not been evaluated in other populations, which could show that their diagnostic performance may be decreased from a development step as the previous report.[8] To be a screening tool for detecting early PsA in psoriasis population, the sensitivity of the test might be more important than the specificity.[15] These screening tools are designed to identify Ps patients with probable PsA that need to be evaluated by a rheumatologist. Detection of PsA at an early stage and treatment may result in preventing deformity and good function.[16] In addition, the performance of the screening tools may depend on ability to detect all patterns of PsA.[8] The sensitivity and specificity of EARP and SiPAT for detecting PsA were good and comparable, regardless of PsA patterns in this study. Conversely, the PEST had much lower performance in detecting axial inflammation than EARP and SiPAT. It may result from EARP and SiPAT capturing all three main patterns of PsA while PEST has no question assessing spinal inflammation.

The pathogenesis that contributes to the development of PsA needs to be further elucidated. Four large cohort studies revealed increasing BMI, smoker, and excessive alcohol consumption to be significantly associated with the development of PsA.[17] The diagnosis of PsA in those four cohort studies was based on medical code and patient self-report verified by PASE tool. Moreover, previous case-control studies which PsA were diagnosed by a rheumatologist using CASPAR criteria reported scalp psoriasis, intergluteal and/or perianal psoriasis, >3 affected sites, nail dystrophy, injuries, infections that required antibiotics, and heavy lifting to be significantly associated with the development of PsA; however, the reported associations were inconsistent among studies.[17] The observed variation in associations may be due to variations in patient characteristics. In the present study, we found only severity of Ps (BSA involvement more than 10%) to be an independent predictor of PsA in multivariate analysis which the same as Haroon, *et al* 'study.[8] The mentionable limitations of this study include those associated with studies with a cross-sectional design, including lack of temporal association (risk factors and disease are measured at the same point in time), and a small study population from a single center compared to the larger populations enrolled in multicenter cohort studies.

In conclusion, the results of this study revealed the SiPAT screening tool to have a relatively high sensitivity for detecting PsA in patients with Ps in an outpatient dermatology clinic setting. Although the pathogenesis of PsA and the risk factors for the development of PsA both need to be further studied and elucidated, the findings of our study suggest that treatment of skin psoriasis may prevent the development of PsA.

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The Development of Personalized Medicine: Acute Myeloid Leukemia as a Model

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ABSTRACT

The term personalized medicine has been employed in widely different contexts and has acquired status as one of the most often used keywords recently. In this review we take it to understand the application of modern diagnostic medicine and therapeutics to patient with the purpose of eradicating disease or alleviating symptoms in a manner, where all actions are based on detailed knowledge of the condition of the individual patient. Applying these concepts should lead to optimization of clinical decision-making and, in its utmost consequence, a substantial decrease in costs incurred for hospitalization and follow-up. The latter is based on the evidence that for many disorders "less but more targeted" will mean improved outcome. Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is a major challenge in terms of diagnosis, care, follow-up and therapy. Thus, in population-based analyses, overall survival is only just exceeding 40% with major reasons for treatment failure. For these reasons, AML has been intensely studied during the recent decades. With the development of multiparametric flow cytometry, it allows us to get an accurate diagnosis and immunophenotypic profiles of AML. In addition, there is now an abundance of knowledge regarding its cytogenetic and molecular background. These enable us to follow the amount of disease down to the minutest quantity with a high resolution of molecular details. Finally, based on knowledge of these variables in the single patient cytoreduction is now being refined to therapies targeted to the molecular changes in the patient.

Keywords: Acute myeloid leukemia; developing country; precision medicine; targeted therapy; Thailand (Siriraj Med J 2019; 71: 414-425)

INTRODUCTION

Acute myeloid leukemia (AML) is a highly malignant blood cancer characterized by rapid accumulation of abnormally differentiated immature myeloid cells in the bone marrow (BM) and peripheral blood (PB), resulting in disruption of the production of normally functioning blood cells.[1] Thus, patients present with severe symptoms of BM failure, *i.e.* anemia, bleeding and often life-threatening infections. AML can arise *de novo*, secondary to antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN), known as secondary acute myeloid leukemia (sAML), or following cytotoxic therapy (tAML). The incidence of AML is generally reported to be 3-5 per 100,000 per year, but varies according to age and study. Despite the fact that initial therapy induces complete remission (CR) in up to 80% of patients, the relapse-rates are high in AML other than acute promyelocytic leukemia (APL) subtype. The

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five-year survival rate of younger patients (age < 60 years) is approximately 40% and less than 20% in the elderly.[2] Unfortunately, data from less developed countries, such as Thailand, showed an even worse outcome. The 2-year overall survival (OS) rates of younger and elderly groups in Thai AML patients were merely 28.6% and 10.3%, respectively.[3] Surprisingly, the Thai cohort showed a lower proportion of patients with good-risk cytogenetics in comparison to other reports.[3]

The diagnostic tool box in AML

There are several diagnostic tools that should be included in the investigation of newly-diagnosed AML patients (Fig 1). Firstly, blast counts from PB and BM smear are simple assays and instantly provide the provisional diagnosis of AML. Standard guidelines recommend counting from 200 total white blood cells from PB or 500 total nucleated cells from BM smear.[4,5] 20% myeloblasts or more in PB or BM is compatible with AML; however, physicians should keep in mind that AML can be diagnosed in the patient who has t(15;17), t(8;21) or inv(16) – even if blast count is less than 20%.[4,5] In addition, for AML-M4, a total blast counts must include monoblasts and promonocytes.

Secondly, immunophenotyping from multiparametric flow cytometry (MFC) is an essential investigation for AML subtype categorization. However, it is required that the MFC machine should be well-equipped with ≥2 lasers and ≥6-8 photomultiplier tubes and operated with technical expertise. Immunophenotypic markers can separate precursor-, granulocytic-, monocytic-, megakaryocytic- and erythroid lineages. MFC is an important part of the diagnostic work up in daily clinical practice, as it provides a rapid blast count together with immunophenotyping capable of confirming the myeloid origin of blasts. In some cases, the immunophenotype can be indicative of underlying cytogenetic aberrations, e.g. co-expression of the lymphoid marker CD19 on myeloid blasts in t(8;21) AML or lack of CD34 and HLA-DR antigens in APL.[6] Moreover, a baseline immunophenotypic result before treatment is important for treatment response evaluation and measurable residual disease (MRD) monitoring.[7-9]

Cytogenetic and molecular analyses are also required for all newly-diagnosed AML to predict patient prognosis and guide treatment decision.[4] Besides, these genetic data are also used to further classified patients into different subtype according to WHO 2016 classification criteria.[10]

The molecular panel that is mandatory to be screened by polymerase chain reaction (PCR) based method includes *PML-RARA, CBFβ-MYH11, RUNX1-RUNX1T1* and *BCR-ABL1* genes. In addition, other gene mutations

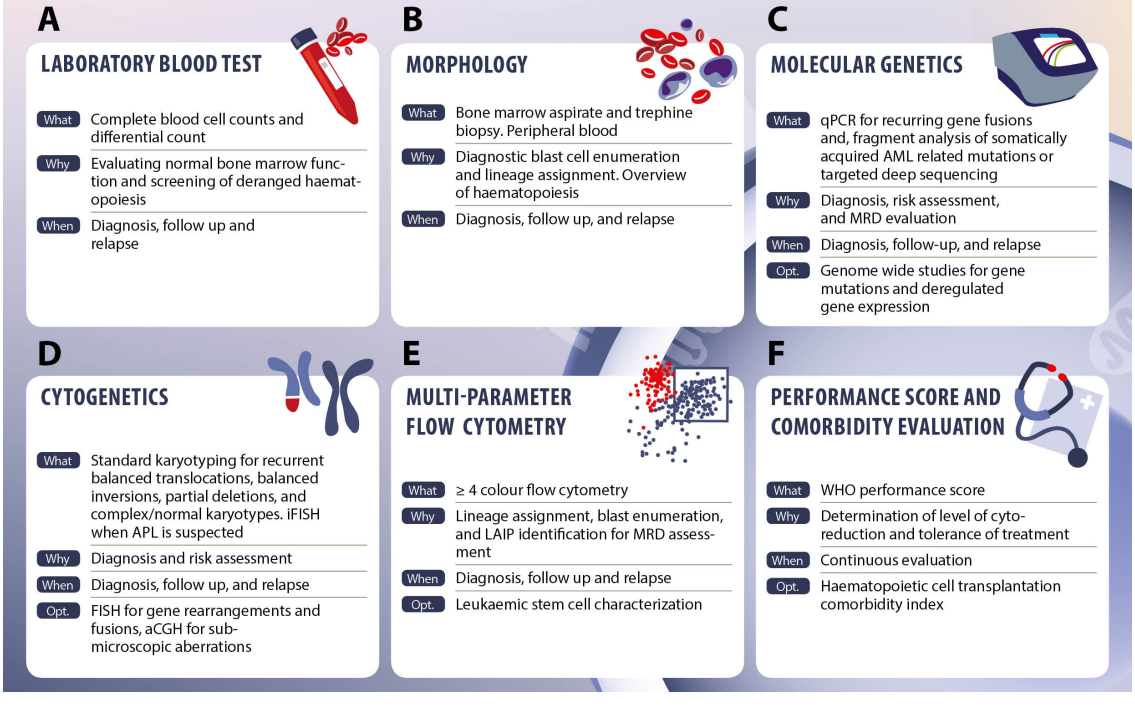


Fig 1. The diagnostic toolbox in acute myeloid leukemia. Blood counts **(A)** and morphology of peripheral blood and bone marrow **(B)** are still frontline assays, when diagnosing acute myeloid leukemia, whereas as molecular genetics/genomics **(C)**, cytogenetics **(D)**, flow cytometry **(E)** are of highly important for subtype classification and prognosis. This information, together with performance score **(F)**, forms the basis of clinical decision-making and treatment strategy for the individual patient. Cytogenetics are also used in diagnosis as specific chromosomal aberrations may override the lower threshold of blasts in the peripheral blood or bone marrow.

including *NPM1, FLT3*-ITD, *CEBPA, KIT, RUNX1, TP53, ASXL1, IDH1* and *IDH2* genes are also highly recommended from the latest standard guidelines as an initial investigation.[4,5] The turn-around time of these workups should not exceed more than 3 days for fusion gene rearrangements, *NPM1* mutation and *FLT3*-ITD mutation and not more than one week for cytogenetic analyses.[4] More advanced technologies, such as next-generation sequencing (NGS), is also now integrated for molecular characterization of AML patients.[11,12] With this method, we can obtain multiple or complete mutational data in a single assay. In the future, we plan to expand the molecular work-up for Thai patients to see if there are any population-based differences from other ethnicity cohorts. This information may arguably be useful in the personalized therapy era. In addition, cost-effectiveness of generalized NGS for routine implementation is to be validated. Table 1 illustrates diagnostic tools for newly-diagnosed AML patients.

While previous prognostic classification systems have primarily been based on cytogenetic findings[13], the revised risk stratification from the European Leukemia Net (ELN) incorporates the most significant prognostic mutations[7] (Table 2).

Genetic risks along with patient related factors, *e.g.* age, comorbidity or performance status, and post-treatment factors, such as the presence or absence of MRD[7], guide the choice and intensity of therapy, which will be discussed further.

Conventional treatment and follow up in AML

While targeted therapy is evolving rapidly for hematological malignancies, the general treatment of AML has not changed substantially the past 30 years.[2] For patients with AML eligible for intensive chemotherapy, standard regimens consist of 1-2 courses of chemotherapy to induce complete remission (CR). CR is defined by a presence of less than 5% blasts in BM accompanied by a complete hematologic recovery. The most commonly used regimen for AML other than APL subtype, referred to as the *7+3 regimen*, is comprised of 7 days continuous intravenous cytarabine infusions and 3-day anthracycline infusions.[11,15] The response is evaluated two weeks after the onset of chemotherapy. Younger and physically fit patients, belonging to intermediate or adverse risk groups, will be referred for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first CR. Patients with favorable risk or without donor eligibility may continue to receive further 2-4 cycles of consolidation chemotherapy. Older patients, not eligible for intensive treatment, will receive best supportive care, *e.g.* low-dose cytarabine (LDAC) or alternatively therapy with a hypomethylating agent (HMA) such as 5-azacitidine[4]. With the continuously poor outcome for AML-patients,[13] it is clear that new and better treatment options are warranted in order to improve survival. In that regard, targeted treatment strategies are attractive in order to obtain efficient kill of the leukemic cells without extensive toxicity on normal cells.

TABLE 1. Diagnostic tool for newly-diagnosed AML patient.

Strongly recommended	**Turnaround time**
Complete blood count with blood smear	1 hour
Bone marrow aspiration for assessment of blast number	1 day
Multiparametric flow cytometry	3 days
Screening for gene rearrangements including *PML-RARA, CBFβ-MYH11, RUNX1-RUNX1T1* and *BCR-ABL1* genes by RT-PCR	3 days
Cytogenetics	7 days
Mutations of NPM1 and FLT3-ITD	3 days
Recommended or optional	**Turnaround time**
Specific gene mutations including *CEBPA, KIT, RUNX1, TP53, ASXL1, IDH1* and *IDH2* genes	7-14 days
Next-generation sequencing for myeloid panel	7-14 days

TABLE 2. Risk stratification according to the 2017 ELN guidelines.

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with FLT3-ITD^{low}
	Bi-allelic mutated *CEPBA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	Inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM(EVI1)*
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype, monosomal karyotype
	Wild-type *NPM1* and FLT3-ITD^{high}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

Modified from[4], where further details are available

Taking aim at personalized therapy in AML: clinical considerations cost-benefit

In contrast to the stagnant situation in conventional induction cytoreduction in AML, treatment therapies are now becoming more personalized. In recent years, much focus has been put on mapping genetic and epigenetic heterogeneity of the malignancies. Consequently, the information of specific antigens expressed on leukemic cells together with somatic mutations have been included in drug investigations to improve outcomes in AML.[16] The treatment approaches are summarized in Fig 2 and 3.

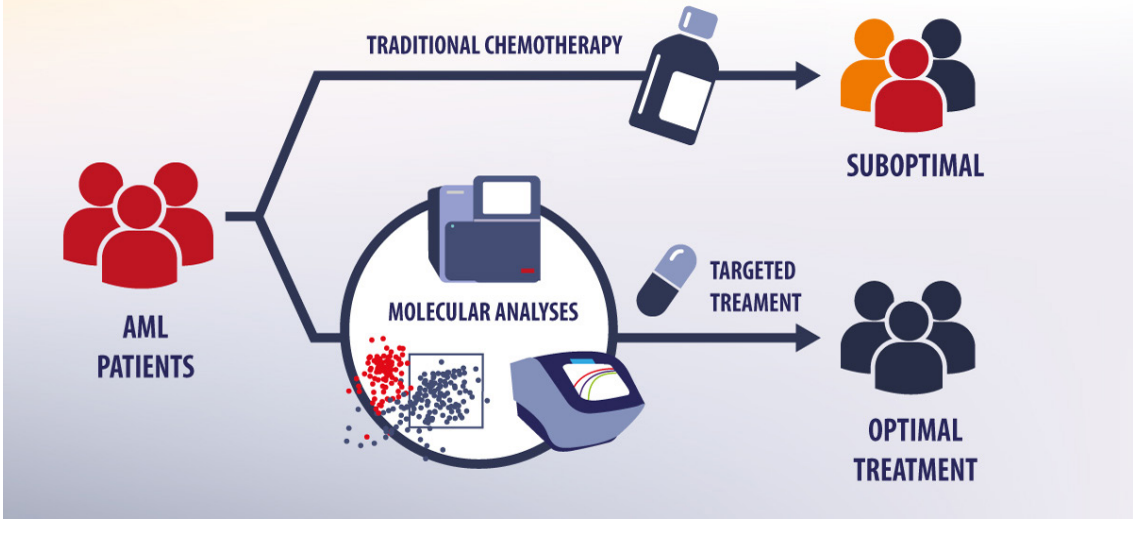


Fig 2. Chemotherapy versus targeted treatment. Targeted therapy is based on the most optimal individual treatment for specific types or combinations of molecular aberrations. The current molecular diagnostics toolbox to guide precision medicine includes both next generation sequencing, digital droplet PCR and flow cytometry, each with different sensitivities, strengths and weaknesses.

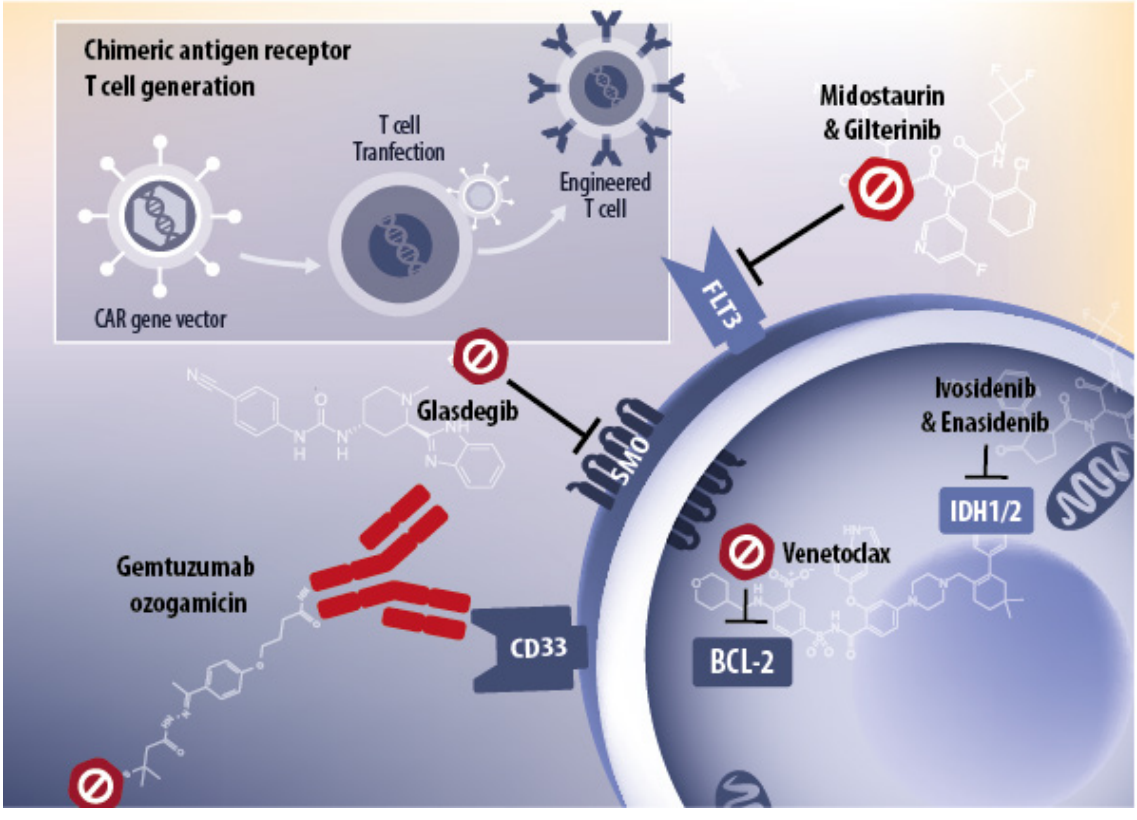


Fig 3. Examples of targeted therapy in acute myeloid leukemia. Targeted therapy or precision medicine has the purpose of eradicating leukemic cells with specific molecular aberrations without hitting nonspecific targets, such as normal hematopoietic cells. These drugs include monoclonal antibodies, such as antibody-drug conjugate gemtuzumab ozogamicin (Mylotarg), which targets CD33, or selective small molecule inhibitors, such as venetoclax for older patients that respond poorly to standard therapy. Other promising strategies of precision medicine include the use of chimeric antigen receptor T cells, where patient T cell are engineered to target the malignant cells (insert).

The studies on novel therapeutic targets, including surface antigen, driver oncogenes and cellular pathways have been an active field of AML research in recent years. Thus, there are many pathway specific agents and chemotherapy with new drug delivery system being approved by the US Food and Drug Administration (FDA). These include midostaurin, CPX-351, enasidenib and gemtuzumab ozogamicin in 2017 and glasdegib, venetoclax, ivosidenib, and gilteritinib in 2018. Here, we review the data of these promising agents along with the benefit to the patients.

Approved drugs

FMS-like tyrosine kinase 3 (FLT3) Inhibitors

FLT3 mutations are found in 30% of AML patients, leading to ligand-independent activation of the receptor, thereby promoting proliferation, survival, and resistance to apoptosis. It is known that patients with a *FLT3* mutations have significantly lower OS.[17] Several drugs that can inhibit FLT3 kinases have been tested in AML. Midostaurin works through inhibition of multiple receptor tyrosine kinases including the activity of wild-type FLT3 and kinases with either internal tandem duplications (ITD) or a mutated tyrosine kinase domain (TKD). In phase III study, where the drug has been given in addition to standard chemotherapy and as a maintenance therapy, OS and event-free survival (EFS) were significantly higher in comparison to placebo (74.7 vs. 25.6 months and 8.2 vs. 3 months, respectively).[18] Due to its survival benefit, US FDA has approved its use in combination with standard induction and consolidation therapy in adults with newly diagnosed AML, who are *FLT3*-mutation positive. Another approved agent is gilteritinib. Gilteritinib is a highly potent inhibitor which has been approved in fast track according to preliminary phase I/II data.[19] Nonetheless, the drug as a monotherapy ultimately showed improved survival in relapsed or refractory AML patients with *FLT3*-mutation in comparison to standard chemotherapy (9.3 VS 5.6 months) in complete Phase III analysis. However, long term survival was still uncommon on either treatment arm. The longest survival in the gilteritinib arm was seen among patients

who underwent HSCT followed by maintenance therapy. Therefore, ongoing study has been done to see whether using the drug as a first-line treatment would give more survival benefit to the patients. Other drugs in this category including sorafenib, quizartinib and crenolanib, have shown benefit in preclinical and early clinical studies and awaits for further validation in various settings.[20]

Isocitrate dehydrogenase (IDH) Inhibitors

IDH1 and IDH2 are enzymes that catalyze the conversion of isocitrate to α-ketoglutarate. *IDH1* and *IDH2* mutations occur in 5-10% and 10-15% of adult AML patients, respectively, with higher frequencies in older patients. These result in an abnormal enzyme activity, lead to the competitive inhibition of α-ketoglutarate dependent enzymes, target genes hypermethylation and impaired hematopoietic differentiation.[21] So far, two agents targeting these mutant enzymes have been approved. The first drug, enasidenib, which is a selective IDH2 inhibitor, provided overall response rate (ORR) of 40.3% and impressive median time to first response of 1.9 months in relapsed and refractory AML patients.[22] Data also confirmed that enasidenib can salvage a number of patients (50% ORR) and provided survival benefits.[23] There is one particular study of enasidenib in newly diagnosed elderly patients, which showed that there were relatively low toxicities (cytopenic rate 21%), good response rate (30.8%) and acceptable OS (11.3 months). Ivosidenib, on the other hand, inhibits *IDH1* mutant enzyme, demonstrated ORR of 42% and CR of 22% in relapsed and refractory AML patients.[24] Therefore, both were approved for treatment of relapsed or refractory AML with a corresponding *IDH* mutation. The durations of responses varied from an average of 6 months to more than 2 years. Additional studies will give more information on the benefit of these drugs in terms of a long-term survival as a frontline treatment. Studies has now been expanded to test these drugs in combination with chemotherapy in newly diagnosed patients and gave a promising results.[25]

B-cell leukemia/lymphoma-2 (BCL2) inhibitor

Venetoclax is a selective, oral small-molecule *BCL-2* inhibitor, leading to cell apoptosis[21] (Fig 3). *BCL2* is overexpressed in hematologic malignancies and implicated in AML cell survival, chemoresistance, and is linked to poor OS in AML patients.[26] As a monotherapy, it demonstrated activity in relapsed refractory or unfit AML (19% overall response rate) with a tolerable safety profile.[27] *IDH* mutational status was correlated with good responses, however, all patients eventually relapse despite the initial response. Lately, the studies showed that rapid resistance may occur from *MCL1* and *BAX* upregulation. Many agents can reduce *MCL1* expression in vitro including chemotherapy and HMA.[28] Venetoclax in combination with HMA in newly diagnosed elderly AML patients demonstrated 67% CR and median OS of 17.5 months.[29] The responses occurred in patients with poor risk mutations; *TP53* and *FLT3* mutations, similar to those with *IDH* and *NPM1* mutations. These impressive results led to recent approval of drug combination with HMA or LDAC for frontline treatment of elderly unfit patients. New combination therapy such as MCL1 inhibitor and IDH inhibitors are lining up to be tested.[28]

Glasdegib

This drug works through inhibition of sonic hedgehog pathway in leukemic stem cells (Fig 3). In phase II, randomized, open-label, multicenter study, 132 patients with AML or high-risk MDS unsuitable for intensive chemotherapy were evaluated for the efficacy of glasdegib plus LDAC in comparison to LDAC alone.[30] It showed OS benefit (8.8 vs. 4.9 months) and clinical efficacy across patients with diverse genetic profiles.[30] This led to its approval by US FDA in 2018 as a treatment in unfit AML/MDS patients.

CPX-351

CPX-351 is a dual-drug liposomal encapsulation of cytarabine and daunorubicin packaged at a synergistic dose of 5:1 molar ratio.[31] A nanoliposomal carrier of the drug leads to prolonged exposure and intracellular delivery. In comparison to a conventional 7+3 induction of cytarabine and daunorubicin treatment in high risk elderly AML patients (60–75 years of age), CPX-351 arm demonstrated higher CR and CR with incomplete recovery (CRi) (57% vs 40% and 73% vs 52%) and led to higher number of patients undergoing HSCT. CPX-351 also improved OS compared with 7+3 (median OS 9.56 vs 5.95 months), regardless of age, therapy-related or MDS-related subgroup.[32] Consequently, it has been approved as a frontline treatment in patients of all ages with therapy-related AML or AML with MDS-related changes.

Gemtuzumab ozogamicin

CD33 antigen is a transmembrane receptor and myeloid differentiation marker variably expressed on AML cells in almost all patients.[33] Gemtuzumab ozogamicin is a humanized CD33 antibody-toxin conjugate toxic to CD33-expressing leukemic cells[32] (Fig 3B). After binding to the antigen on the surface of leukemic blasts

the antibody is internalized and binds to DNA leading to double-strand break and cell death. It has been previously withdrawn from American market in 2010 due to its toxicity and limited benefit.[34] However, with recently more efficacy data and desperate needs to improve treatment of elderly AML patients, the drug has been resubmitted to US FDA regulatory review again.[35] In newly diagnosis adult AML patients age 50 to 70 years, a randomized phase III trial of daunorubicin and cytarabine with or without gemtuzumab ozugamycin in induction and consolidation chemotherapies (ALFA-0701) has shown the benefit of increase median EFS of 15.6 months in the gemtuzumab ozogamicin arm versus 9.7 months in control arm except in patients with adverse cytogenetic risk.[36] In addition, in de novo or sAML patients age >75 years or age 61-75 years with WHO performance status >2 who are unwilling to receive intensive chemotherapy, gemtozumab ozogamycin monotherapy resulted in a significant improvement in median OS 1.3 months comparing to best supportive care arm. The toxicities did not differ between treatment arms.[37] This agent was approved in newly diagnosed CD33-positive adult AML and relapsed or refractory CD33-positive AML in adult and pediatric AML aged 2 years and older.[35] New CD33 antibody and drugs targeting CD33 are currently tested in various studies.[38]

Investigational therapy

Cellular therapy targeting surface targets

Chimeric antigen receptor T cell (CAR-T) therapy targeting surface marker of AML, e.g. CD33, CD123 and FLT3, have been developed in preclinical and early clinical phase with some concerns of serious toxicities.[39] Many leukemia associated antigens are differentially expressed by MHC on tumor cells and have been investigated in small clinical studies to be used as a vaccine or dendritic cell-based therapy. These targets include Wilm's tumor 1 (*WT1*), New York esophageal squamous cell carcinoma 1 (*NY-ESO1*), PRAME and survivin (*BIRC5*).[40] However, the main challenge of vaccine-based therapy is MHC restriction. Immune checkpoint inhibitors are also of great interests and have currently been studied in different combination at various phases of treatment.[41]

Ongoing investigation therapies

Many more inhibitors that targeting different pathways such as DNA repair and epigenetic modification, including polyadenosine diphosphate ribose polymerase (PARP), lysine-specific demethylase 1 (LSD1), bromodomain and extra terminal (BET) and mutant TP53 pathway have now been tested in clinical studies.[41,42]

Innovative approach for precision medicine

As a result of novel targeted therapy discovery, we may select the proper treatment to the patients according to their molecular abnormalities. Not only specific mutation can be targeted directly but rather several features can also predict drug response. For instance, co-occurring *IDH2* and *DNMT3A* mutations result in distinct DNA methylation pattern, leading to upregulation of RAS signaling and sensitivity to *MEK* inhibition.[43] This proved to be feasible in Beat AML study which included 273 elderly patients. Ninety-five percent of the study group could be assigned to treatment by mutation stratified algorithm within 7 days.[44] Apart from matching genetic data to targeted therapies, drug sensitivity testing (DST) approaches such as ex vivo drug sensitivity screening can guide the individualized treatment more precisely. By using a sample from each patient tumor as an avatar to evaluate patient-specific drug sensitivity profiles. This method is attractive due to easy accessibility of malignant cells in the PB or BM and will be very useful – especially for relapse/refractory patient. Preliminary data from a pilot study showed that it can be done within short turnaround time. Even though initial results have showed a promising outcome, further studies should be performed.[45] However, due to molecular heterogeneity of AML, possible target mutations may be one of several potential targets. Many challenging questions still need to be answered including how to identify the key pathway, whether a combination of targeted drug would be beneficial and how to manage the toxicities.

Costs of novel treatment in AML and clinical benefits

Advanced therapies have changed the way of treatment especially to patients with high risk features who have low chance of survival. Most of them are currently approved to be used as a last resort in patients who fail or deem unsuitable to conventional treatment. Even though they provide more opportunities to increase OS the treatment, however, rarely lead to cure as monotherapy. These effective drugs also come with high costs leading to an increase of the economic burden in AML treatment. The prices of these drugs are summarized in Table 3. In countries with limited resources treatment decision should always be made by evaluating the cost-effectiveness to patient survival and quality of life. Choosing a drug, which provides the best response to the right group of patients at the right time and administered in a brief duration as a bridging therapy to curative HSCT, would be the most optimal way to limit costs and provide the best outcome. In contrast, we can save cost by not giving

TABLE 3. Novel drug costs in AML: dose recommendations and average prices.

Drug name	Dose recommendations	Average price*
Midostaurin (FLT3 inhibitor)	50 mg twice daily, days 8–21 of induction and consolidation	5,448 baht per 25-mg tablet
Gilteritinib (FLT3 inhibitor)	120 mg once daily	9,600 baht per 40 mg
Enasidenib (IDH2 inhibitor)	100 mg once daily	32,953 baht per 100 mg
Ivosidenib (IDH1 inhibitor)	500 mg once daily	16,713 baht per 250 mg
Venetoclax (BCL2 inhibitor)	Day 1, 100 mg once daily Day 2, 200 mg once daily Day 3, 400 mg once daily Day 4 and beyond, 400 mg once daily	357 baht per 10 mg 1,784 baht per 50 mg 3,568 baht per 100 mg
Glasdegib	100 mg once daily	10,832 baht per 25 mg
CPX-351	Induction, 44 mg/m^2–100 mg/m^2 on days 1, 3, 5 Reinduction (if patient not in remission), 44 mg/m^2–100 mg/m^2 days 1, 3 Consolidation, 29 mg/m^2–65 mg/m^2 on days 1 and 3 for 2 cycles	306,528 baht per 44–100-mg vial
Gemtuzumab ozogamicin (humanized CD33 antibody-toxin conjugated)	Induction (incombination with "7+3" regimen, 3 mg/m^2 (max 4.5mg/dose) on days 1, 4, 7 Consolidation, 3 mg/m^2* day 1	314,880 baht per 4.5-mg vial

*Costs are reported as average wholesale price and calculated from US dollar price (1 US dollar equals 32 Thai Baht). They are not meant to represent true costs.
Modified from[46]

drugs to patient with predictive low response profile. Nowadays, technologies for precision medicine, and especially next generation sequencing, have become much more accessible than a decade ago. With more information and tools, they will guide the clinicians to the treatment that provides maximum benefits – not only as a salvage but as a frontline therapy. If we can use these regimens upfront, we may prevent more patients from relapsing and avoid the side effects and costs from chemotherapy and HSCT. Nevertheless, novel therapies give us treatment options, which were previous unavailable, and possibly with new side-effects. Therefore, information with regards to risks and benefits should be given to the patient and should be able to reach a final decision that match their interests and expectations under solid counselling from the clinician.

Follow-up in the age of personalized medicine

Relapse in AML patients may be caused by a persistence or an evolution of therapy-resistant leukemic clones in the bone marrow. To capture low level of cancer cells, referred to as MRD, high sensitivity laboratory investigations are required. As discussed above, relapse is still common even in patients who have reached CR states. The goal of MRD monitoring is early detection of patients at risk and guide treatment decisions to minimize the risk of clinical relapse by intensifying the therapy. Alternatively, in the era of targeted therapy, we may be able to target the specific pathway in resistant leukemic clones. Conventional methods using morphology and cytogenetic assay have low sensitivities and only allow the detection of leukemic cells greater than one cell in 20 leukocytes. Therefore, even in a CR state, up to 1011

residual leukemic cells may still exist.[47] Currently, two widely accepted methods to detect MRD are; MFC and real time quantitative PCR (RT-qPCR) which can detect MRD leukemic cells in white blood cells component with a sensitivity down to 10^{-3} – 10^{-6}.[48] However, MRD detection is not a straightforward process, because of the immunophenotypic and molecular heterogeneity between patients and clonal heterogeneity that may emerge as novel resistant clones under selective pressure – especially in response to single targeted therapy.[49,50] Identifying the appropriate markers that differentiate leukemic cells from normal hematopoietic progenitor, to evaluate disease burden or MRD and to predict relapse, is still challenging. Follow-up approaches are summarized in Fig 4.

Multiparametric flow cytometry

By labelling cells with multiple fluorescent markers and determining the light emission from the cells as they flow against laser beam, MFC can characterize phenotypes and immunophenotypes of malignant cells down to a single level. Apart from being used as a diagnostic tool, MFC can also be used as a disease monitoring method. MFC has the sensitivity to detect MRD of leukemic cells down to 10^{-3}-10^{-5}.[48] It can be applied for almost all patients. However, due to the complexity of leukemic immunophenotype described previously, the markers need to be tailored. A large panel of antibodies of more than 8 colors are recommended for characterizing the leukemic cells by MFC. The marker should include early hematopoietic markers (e.g. CD34, CD45, CD117), myeloid-lineage associated markers (e.g. CD4, CD11b, CD11c, CD33, CD64), aberrant differentiation markers (e.g. CD2, CD7, CD19, CD56).[51] MRD can be defined by either tracking leukemia associated immunophenotypes (LAIP) from the diagnosis or by identifying new emerging clone that express aberrant differentiation profiles called different-from-normal (DfN) approach. ELN MRD working party recommends a combination of both approaches to best define MRD burden.[51] Other markers that could be used to define leukemic stem cell population, e.g. CD38, CD123, CD133, are also of interests. There are also some technical considerations including the source of specimen, sample collection and number of collected cells. For example, MRD level in PB may be one-tenth the frequency in BM. Therefore, a detection of MRD by MFC in PB is not currently recommended and bone marrow specimen should be collected from the first pull to avoid hemodilution. Because of the complicated process and interpretation, a validation of the method is essential. It

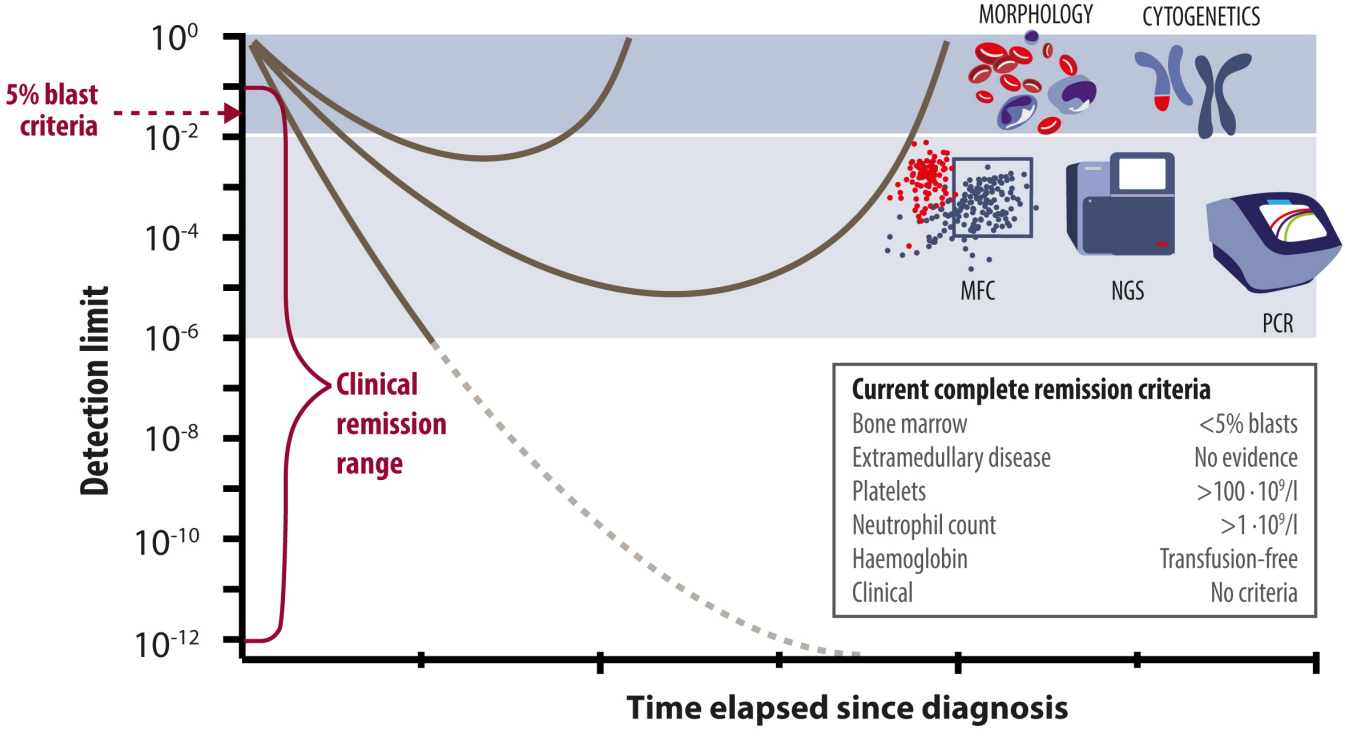


Fig 4. Detection of minimal/measurable residual disease (MRD). Currently, PCR is still the most sensitive method to detect MRD. Next generation sequencing (NGS) is being investigated as a potentially highly sensitive method for detection of residual disease, while increasing the informational content for clonal assessment.

is recommended that there should be a central institute for an evaluation and a final interpretation and should not be done in a single-centered fashion. Various cut-off values have been applied but MRD level below 0.1% is the most widely used in the clinical studies, with more than 500,000 CD45+ cells acquired.[51]

Molecular MRD

Molecular abnormalities of the leukemic cells can be used as a marker to monitor the level of malignant cells with the help of PCR-based methods. qRT-PCR is a laboratory technique based on the PCR to measure the amplification of a targeted DNA molecule during the PCR in real-time. It can be used quantitatively or semi-quantitatively. This approach has a high sensitivity for detecting one malignant cell in 10^4 to 10^6 leukocytes. It can detect target genes representing malignant cells and is considered as the gold standard for MRD detection. However, in contrast to MCF, this approach is applicable for only around 40% of patients who have suitable abnormalities. Target genes could be fusion, recurrent mutated or overexpressed genes. However, only some verified markers associated strongly with relapse including *NPM1* mutation, *RUNX1-RUNX1T1, CBFB-MYH11* and *PML-RARA* fusion.[51] Some other mutations may persist after treatments but do not relate to real disease burden. For example, mutations that occur in the preleukemic clone which can be found in aging population e.g. *DNMT3A, ASXL1, TET2*[52,53] or in germline e.g. *RUNX1, GATA2, CEBPA, DDX41, ANKRD26*[54]. Apart from those genetic markers, *FLT3*-ITD, *FLT3*-TKD, *NRAS, KRAS, IDH1, IDH2, MLL*-PTD and the expression of *EVI1* are not recommended to use as a single marker but rather in combination.[51] Despite being shown to relate with patient outcome in many studies, using WT1 expression as a MRD marker is still controversial due to its low sensivity.[51,55-57] More recent technologies such as Next generation sequencing (NGS) and droplet digital PCR (ddPCR) are ideal to be used in all patients. NGS gives the whole genetic profile of the patient while ddPCR allows simultaneous multiple gene expression quantification. The main shortcoming of NGS is that it has low specificity in low allelic burden setting.[48] While ddPCR require the establishment of specific set of primers according to sequencing data. Even though promising, more studies is needed to verify and standardize the methods.[58]

CONCLUSIONS AND PERSPECTIVES

AML is often regarded as a signature disease in hematology. Thus, it is the most common leukemia in adulthood and though advances have been made, both in terms of diagnosis, follow-up and therapy, the long-term survival of patients is still unsatisfactory, with treatment failure being the reason. The concepts of personalized and precision medicine have been coined after the availability of genome sequencing and the increased realization that each patient has different in genetic mutational background. A targeted treatment points to the specific mutation which causes better treatment outcome compared to conventional therapy.

The standard AML treatment in last several decades has changed, expecting to improve patient outcomes and quality of life. However, having more available choices might lead to additional concerns, such as drug costs versus clinical significance. Comprehensive or complex decision-making in personalized medicine are highly relevant matters in these situations. However, it is important to note that not all these techniques and the clinical decisions following their results need to increase the costs of treating AML patients. In fact, the presence of some molecular phenotypes, such as the CBF subset, will mean that allo-HSCT is not needed for certain patient groups. In addition, it should be remembered that current therapy of AML, like the time-honored *7+3 regimen*, while not being expensive in term of drugs, is accompanied by very severe side effects, mostly related to the deep immunosuppression and highly correlated with serious bacterial and fungal infection. In this setting, more expensive personalized therapies developed though knowledge about the phenotype and molecular profile of the given patient's malignant cells, might be more efficient and not accompanied by similar side-effect, resulting in fewer days in hospital and minimize antibiotic or antifungal usage. This applies not only to agents targeting molecular drivers, but also to the recently developed therapeutic options relating to redirecting cytotoxic NK- and T-cells (CAR cells) or unmasking immunogenic molecules on the AML cells in the exciting field of checkpoint immunotherapy. In all these situations it is the job of health care providers to enlighten administrators and funding authorities about such potentially cost-saving actions.

It is noteworthy that these issues pertain not only to affluent countries, but equally to those with strained economies. Pharmacoeconomics is to be investigated with regards to appropriation of novel therapy for AML patients in each country.

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Hybrid Central Odontogenic Fibroma with Central Giant Cell Granuloma Like Lesion ; A Case Report and Review of the Literature

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ABSTRACT

The combination of central odontogenic fibroma and central giant cell granuloma is extremely rare and has been reported in only 46 cases worldwide in previous articles. The lesion is called a hybrid central odontogenic fibroma with central giant cell granuloma like lesion (HCOF-CGCG) due to a histopathological characteristics of multinucleated giant cell and odontogenic epithelium in fibro-cellular background. We report a case of HCOF-CGCG in a 27-year old Thai male patient who was identified as the first case in Thailand. Radiographic examination showed a well-defined radiolucency lesion at posterior mandibular area. Enucleation and curettage were done and microscopic study revealed a fibro-cellular proliferating tissue containing numerous strands, cord of odontogenic epithelium, and numerous multinucleated giant cells. This report also included a literature review of the previous 45 cases.

Keywords: Central odontogenic fibroma; central giant cell granuloma; hybrid (Siriraj Med J 2019; 71: 426-431)

INTRODUCTION

The central odontogenic fibroma (COF) is an uncommon disease found in gnathic area.[1] In 2017, WHO defines it as an ectomesenchymal tumor with a mature fibrous connective tissue lesion, which usually combines with an odontogenic epithelium.[2] It can occur in wide-ranging age distribution and slight female predilection affecting relatively equal frequency in both jaws.

The lesion in maxilla usually occurs anterior to first molar and about half of all mandibular lesions are found posterior to first molar.[3] The small COF is often asymptomatic and presents as well-defined unilocular radiolucency whereas the larger lesion may be associated with a pain, a bony expansion, a root resorption, a divergence of adjacent tooth roots, a loosening of teeth and presents as multilocular radiolucency.[3,4]

The histological features of the COF are similar to other tumors including enlarging dental follicle, odontogenic myxoma and desmoplastic fibroma.[5-7] Histopathological features of COF compose principally of mature collagen fibers along with numerous interspersed fibroblasts. In addition, presence of small nests or strands of inactive odontogenic epithelium are found to be a variable feature.[3] It also can present with histological variations such as granular cell, giant cell and pleomorphic fibroblast combination.[8,9]

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Central giant cell granuloma (CGCG) is a benign neoplasm of jaw comprising a giant cell reparative granuloma.[10] The CGCG occurs in around 10% of jaw lesions and is reported to occur often in patients aged below 20 years with female predilection.[2,10] The lesion usually develops in the anterior of the mandible with characteristics of slow growing, asymptomatic, and expansible lesion in nature.[10] The radiographic finding shows the well-defined radiolucency, but it can be multilocular in advanced lesion. About 30% of CGCGs exhibit aggressive behavior associated with pain, root resorption, displacement of adjacent tooth, and cortical perforation.[2]

Histopathological feature of the CGCG is shown with a non-encapsulated proliferation of mononuclear spindle-shaped and polygonal cells with osteoclast-type multinucleated giant cells in a vascular background with hemorrhage and haemosiderin pigment.[10,11] Likewise, there is a similar histological feature between CGCG and giant cell lesion of bone comprising cherubism, hyperparathyroidism, aneurysmal bone cyst and Noonan syndrome.[12-14]

In 1992, Allen reported the first case of hybrid central odontogenic fibroma with central giant cell granuloma like lesion (HCOF-CGCG). The histological finding revealed the fibro-cellular tissue, odontogenic epithelium, and distribution of the giant multinucleated cells.[15] HCOF-CGCG has been reported in only 45 cases worldwide in history and considered as a rare lesion. This study aimed to report a rare case and provide a literature review of HCOF-CGCG.

CASE REPORT

A 27-year-old Thai male was referred by general dentist for management of a radiolucent lesion which was accidentally found on a radiographic examination prior to a third molar surgery. According to a history taking, the patient did not notice the presence of lesion in his lower left jaw and did not report numbness or pain in any area. He also underwent a tooth extraction in this area 3 years ago. Clinical examination found a buccal expansion with obliteration of mucobuccal fold and a root fragment of mandibular left first molar. The teeth involved in this area were vital in response to an electric pulp test.

The routine radiograph (Fig 1A) which was obtained 3 years ago did not present any sign of the lesion, but it presented an endodontic lesion of a first mandibular left molar. Preoperative radiograph (Fig 1B) revealed a well-defined unilocular radiolucent lesion, measuring approximately 18x18 mm, extending from a left mandibular second premolar to left mandibular second molar. The lesion was superimposed with a mental foramen and inferior alveolar canal. The root fragment was identified as a radiopaque mass at superior border of the lesion.

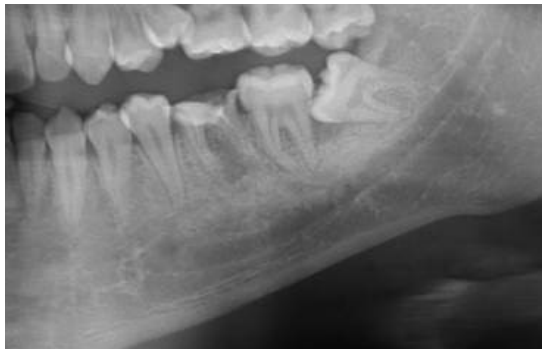


Fig 1A. The routine Panoramic Radiograph 3 years ago.

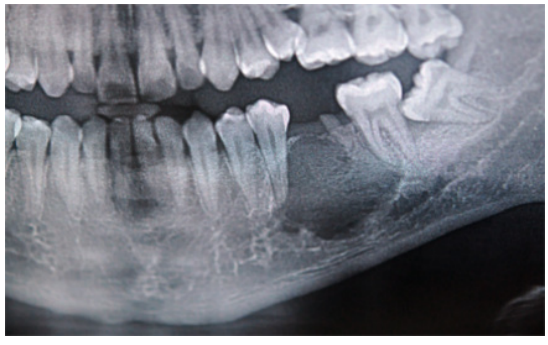


Fig 1B. The preoperative Panoramic Radiograph.

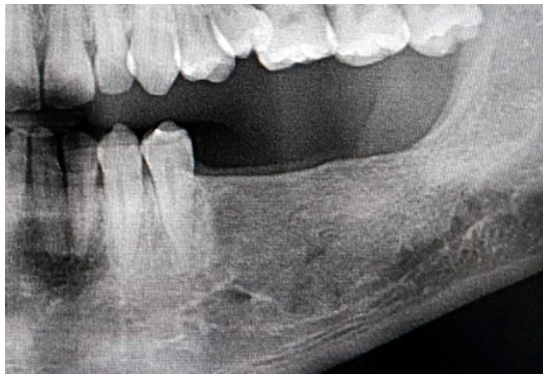


Fig 1C. The 6-month follow-up Panoramic Radiograph.

The differential diagnosis included a radicular cyst, odontogenic keratocyst, and unicystic ameloblastoma. The treatment plan was enucleation by curettage of the total lesion. During the surgical procedure, we found a buccal bone perforation and soft tissue mass within the lesion detached from the surrounding bone. Both inferior alveolar nerve and mental nerve were exposed during the surgery, the inferior alveolar artery was also injured. The bleeding was controlled using bone wax. The lesion was completely removed. The macroscopic appearance (Fig 2) of the lesion was red-pink soft tissue mass with hemorrhage. The primary wound closure with

3-0 silk was done. At one-week follow-up, the patient presented with slight numbness at his lower left lip.

Multiple 4um-thick formalin-fixed paraffin-embedded sections of the specimen were stained with hematoxylin and eosin. Microscopic examination (Fig 3A, 3B) revealed that it mainly composed of a fibrocellular proliferating tissue containing numerous strands, and cord of odontogenic epithelium. Numerous multinucleated giant cells were seen to be dispersed into the connective tissue with a whorled pattern. Small areas of the connective tissue containing odontogenic epithelium and multinucleated giant cells were separated together. Areas of myxoid stroma and hemorrhage were also observed. Immuno-histochemical stains of cytokeratin 19 was used to confirm the structure that mimicked odontogenic epithelium. The immuno-histochemical was positive on cytoplasm of odontogenic epithelial cells (Fig 3C). Morphology was compatible with HCOF-CGCG. At six-months follow up, no evidence of recurrence occurred, both clinically and radiographically (Fig 1C). The numbness was completely resolved.

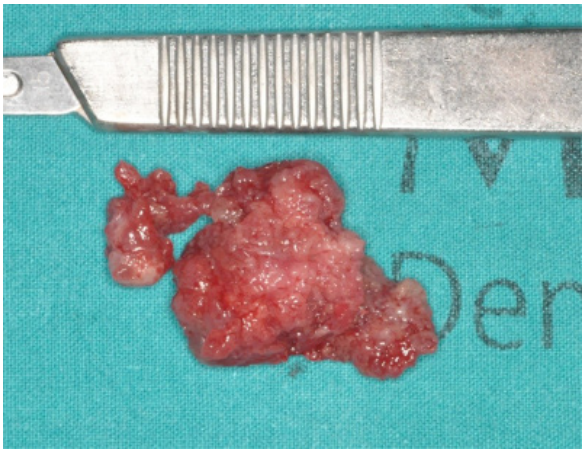


Fig 2. The specimen of the lesion that was completely enucleated.

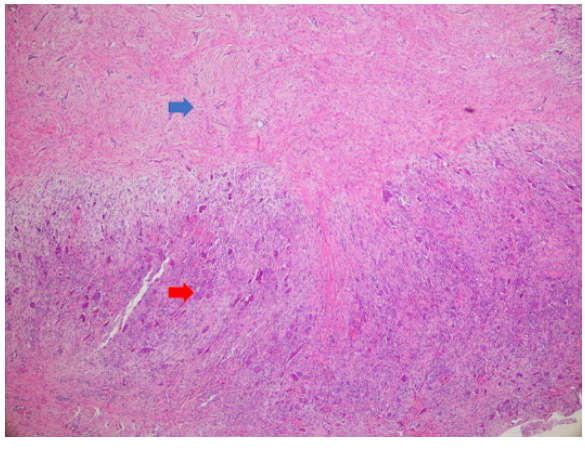


Fig 3A. The histopathology of the combined lesion was composed of areas of giant cell granuloma and odontogenic fibroma. The areas of sole giant cell granuloma (red arrow) and odontogenic fibroma (blue arrow) areas were demonstrate at periphery of the lesion.

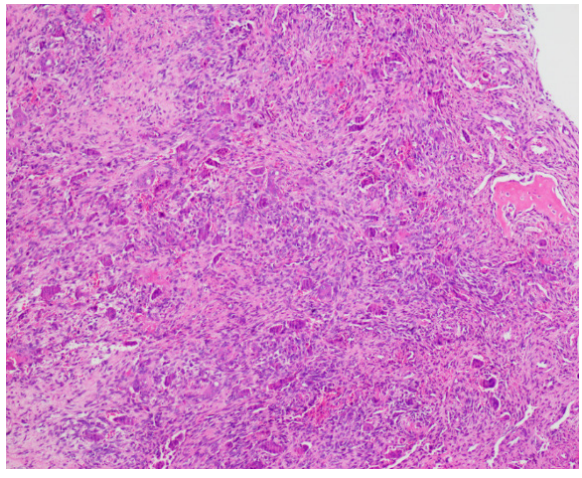


Fig 3B. The histopathology of the areas of giant cell granuloma presented scattering multinucleated giant cells are in the inflamed fibrous tissue.

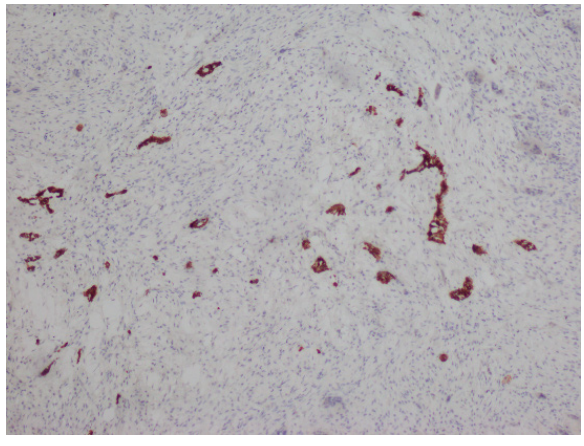


Fig 3C. The histopathology a cytokeratin 19 staining was presented in cytoplasm of odontogenic epithelial rests.

DISCUSSION

The HCOF-CGCG is a rare combination and was first reported by Allen in 1992.[15] The previous reports and the international conferences so far found the number of cases has increased gradually and is reckoned to be 46 cases including this case. The available information of all cases are presented in Table 1. The lesion occurs mostly in second and third decade of life with a female predilection and is more frequent in a tooth bearing posterior mandibular area (86%) alongside the buccal expansion. The tooth displacement is also found in some cases.[16-18] A few cases report the relation of the lesion with an orthodontic, root canal treated tooth, embedded tooth, and cherubism.[15,19,20] There are only 2 cases reporting pain whilst the remaining have been asymptomatic.[9,17]

Radiographically, 60% presented as a well-defined unilocular radiolucency and the rest of the lesions presented with multilocular radiolucency. The ill-defined border characteristic can be found in some cases.[15] The extensive

TABLE 1. Information of previously reported cases.

Case No.	Author/Year	Age/Sex	Location	Clinical features	Radiographic findings	Treatment	Recurrence
1-3	Allen, 1992[15]	3F; 66/14/30	Mandible premolar/molar area	Root canal treated tooth involvement, orthodontic treatment, expansion	Multi/uniloclar	Curettage	Recurrence
4.-6.	Fowler, 1993[24]			Reported 3 cases but no clinical data available			
7-14	Odell, 1997[21]	5F;5/20/21/22/39/43/50, M;11	Maxilla, posterior mandible	Buccal expansion, history of extraction, rapid growth, buccal perforation, tooth mobility	Unilocular	Curettage	Recurrence
15.	Taylor, 1999[9]	17/F	Mandible/ canine/premolar area	Buccal expansion, tooth displacement, thining cortex	Unilocular	Curettage	None
16.	Kruse-Losler, 2006[11]	22/F	Mandible/ from right to left molar area	Lingual and inferior expansion	Multilocular, scalloped border	Surgical excision	None
17-23	Pontes, 2008[1]			Reported 7 cases with 5 males and 2 females at mandible			Recurrence 3 cases
24-30	Tosios, 2008[19]	6M; 18/50/73/15/59/25, F;20	Mandible/ premolar/molar area	Cherubism, perforation	Multi/uniloclar, premolar apex	Surgical excision	None
31.	Younis, 2008[23]	57/F	Mandible/ premolar/molar area	Buccal expansion	Unilocular	Curettage	None
32.	Marina, 2008[16]	24/F	Mandible/ from right to left molar area	Mandibular swelling progressively for 8 years, tooth displacement	N/A	Curettage and reconstruction	None
33.	Bologna-Molina, 2011[22]	14/M	Mandible/ premolar/molar area	Buccal expansion	Multilocular	Resection and reconstruction	None
34.	Castillo, 2011[17]	14/M	Mandible/ molar area	Expansion, tenderness, tooth displacement	Unilocular	Curettage	None
35-36	Eversole, 2011[8]	42/F, 27/F	Body of mandible, Body of mandible and ramus	N/A	N/A	N/A	N/A
37-38	Mosqueda-Taylor, 2011[18]	14/M, 14/M	Mandible/ molar area, Mandible/ premolar/molar area	Both buccal and lingual expansion, tooth displacement, tenderness on palpation, 6 months evolution	Unilocular, Multilocular	Surgical excision	None
39.	Damm, 2013[25]	75/F	Mandible/ anterior	N/A	Unilocular	Curettage	None
40.	Eliot, 2015[26]	22/F	Mandible/ canine/ premolar/molar area	Swelling at mandible and submandibular area	Multilocular	Curettage	None
41.	Schultz, 2017[27]	12/F	Mandible/ anterior	Asymptomatic	Multilocular	Enucleation and selective extraction	None
42.	Leite, 2017[28,29]	42/F	Mandible/ molar area	N/A	N/A	Surgical excision	None
43-46	Upadhyaya, 2018[20]	2M; 10/62, F;63	Mandible anterior, posterior	Buccal and lingual expansion, embedded tooth	Unilocular	Curettage	None
46.	Current case report	27/M	Mandible premolar/ molar area	Asymptomatic, buccal expansion, progression less than 3 years, retained root	Unilocular	Curettage	None

N/A is defined as no available data.
Noted that cases from Fowler and Hassan provided insufficient information but the cases are still accumulated the total number of the cases.

lesions have been reported in a few cases which included a sinus involvement and crossing the midline.[21] Taylor et al., reported that the lesion was distinctive from surrounding bone and had no encapsulation.[9] Also, some authors reported that the lesion caused a bony cortex thinning and perforation.[9,19,21] Most of COF and CGCG, were treated by curettage. One case was treated by resection and reconstruction to prevent a mandibular fracture.[22] The recurrent lesions reported 17% which were treated by curettage. Similar to the nature of COF and CGCG, recurrences have been observed with slightly higher rate in the aggressive behavior, ill-defined margin and multilocular lesions.[1,10,11] Odell et al., stated that the lesion tends to behave like the CGCG much more than the COF due to its prevalence and behavior.[21]

Histo-pathologically, several cases of the HCOF-CGCG were found to be contained as densely collagenous to fibromyxoid stroma with several nests of inactive odontogenic epithelium. The areas have been revealed to merge independently with a variably plump to narrow spindle-shaped fibrocellular connective tissue containing multinucleated giant cells.[18,21,23] Similarly, in this reported case, features of HCOF-CGCG like components and the odontogenic epithelial nests in the mature fibrous connective tissue were seen histologically.

The pathogenesis of hybrid lesion is still unclear. There are 3 theories mentioning the origin.

1. The first theory was proposed by Allen et al, who first reported the hybrid lesion. The theory suggested "collision tumor" which is defined by synchronous occurrence of COF and CGCG. This theory seems seldom to happen and is opposed by recurrent lesion. Almost all the recurrencea presented with combination of COF and CGCG. The combination seems to be a specific characteristic of it.[15]

2. The second theory is "primary CGCG induced secondary COF". This theory stated the cells present within CGCG produce factors like growth factors, chemokines, and cytokines which induce the growth of odontogenic cell line and can result in development of COF.[15]

3. The third one is opposite to the second theory. The primary tumor is COF and the trauma or other stimulus induces a giant cell reaction.[21]

Now, it cannot certainly conclude the origin of this hybrid lesion. The evidences of lesion vicinity, histopathology, and recurrence are a conjecture of the pathogenesis.

According to this current case, the lesion occurred in an early adult male which is different from the other studies. The clinical features were similar to the other reports which are buccal expansion and asymptomatic. The radiographic finding was well-defined with corticated border which corresponded to the characteristics during removal. The lesion showed no infiltration pattern and was detached from the surrounding bone. It caused the buccal bone thinning which is similar other reported cases. In addition, the lesion progressed within 3 years since the past radiograph confirmed the presence of the lesion. In surgical point of view, this intra-bony lesion was easy to remove by enucleation and curettage.

Our opinion suggested a possibility that this lesion could be a "collision tumor". The growth of collision tumor arose from the synchronous occurrence of COF in the same area as a CGCG.[9,21] This theory correlated with our case due to the presence of intrabony mixed-up area of these two lesions. This case displayed three different areas including: odontogenic fibroma, giant cell granuloma and two merged lesions. The sole areas of COF and CGCG were present only at the border of the specimen. The central area of the specimen demonstrated mixed histopathologic features of odontogenic fibroma and giant cell granuloma-like lesion. In conclusion, the HCOF-CGCG was considered as a rare oral lesion. The nature of the lesion was mostly non-aggressive behavior. The treatment by enucleation and curettage seemed to be promising. The histopathological feature was characterized by the presence of the fibro-cellular proliferating tissue containing numerous strands, cord of odontogenic epithelium, and numerous multinucleated giant cells. The presence of COF and CGCG could be merged or independent.

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