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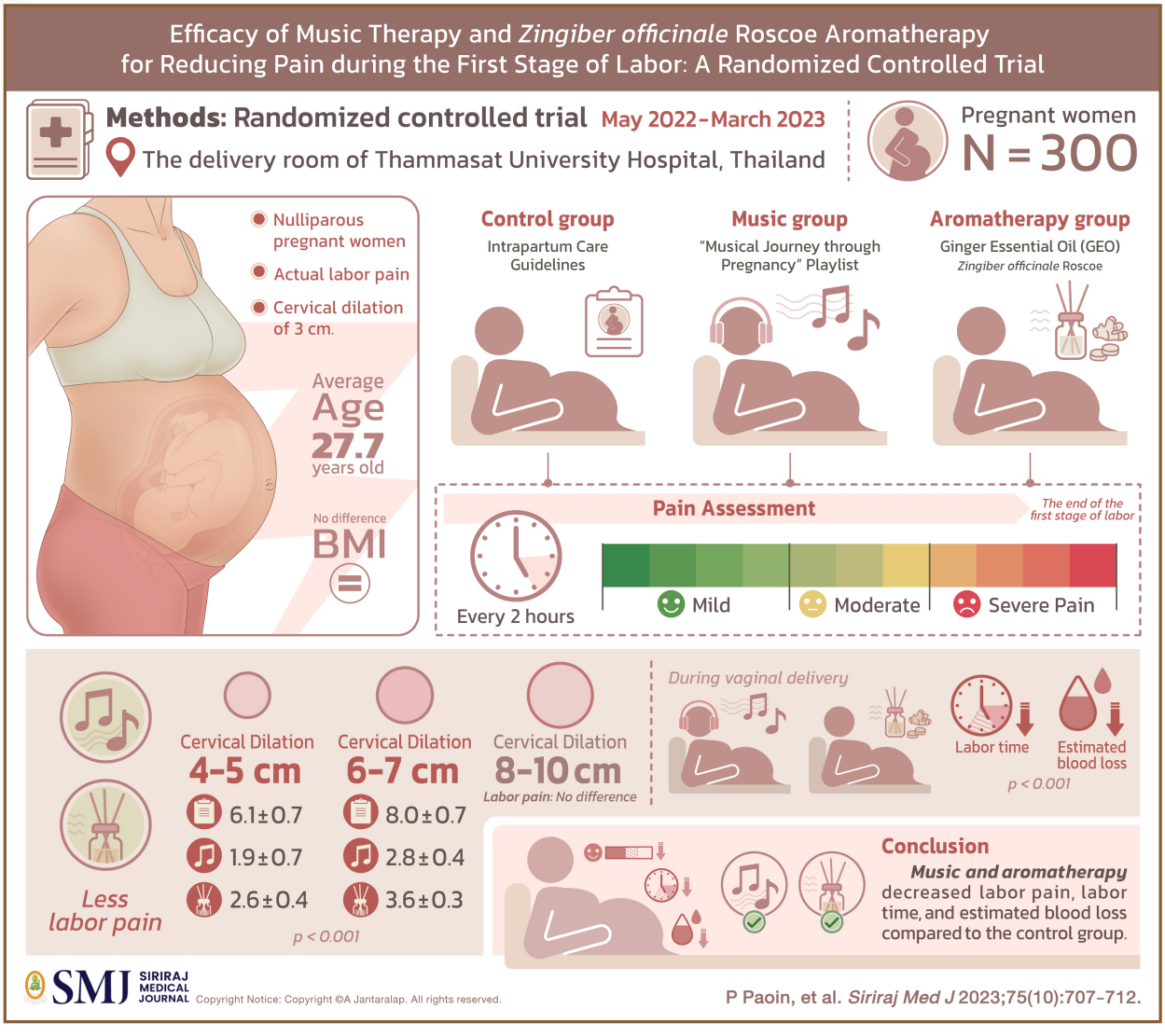

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Prevalence of Urinary Tract Infection in Pregnancies with Premature Uterine Contractions

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ABSTRACT

Objective: This study aimed to determine the prevalence of urinary tract infection (UTI) among pregnant women with premature uterine contractions. Roles of the current practice of routine simultaneous urinalysis and urine culture in these cases were also evaluated.

Materials and Methods: Medical records of pregnant women admitted with premature uterine contractions at Siriraj Hospital between January 2013 and December 2017 were reviewed. Prevalence of UTI in these women was determined. Women were divided into 2 groups based on diagnosis at admission; group 1 included preterm labor/preterm prelabor rupture of membranes (PTL/PPROM), and group 2 was threatened preterm labor (TPL). Evaluations of urinalysis and/or urine culture were performed in these two groups to establish a strategy to reduce unnecessary urine culture.

Results: The prevalence of UTI among 2,286 women with premature uterine contractions was 4.9%. Prevalence of UTI were not different between the two groups of women. A positive urine culture was found in 2.4%. The most common organism identified in both groups of women was *Escherichia coli*. Urinalysis with abnormal cell counts and/or significant presence of bacteria could be used to screen for women in TPL group who should have urine culture with a positive screening rate of 6.5% and 90.9% sensitivity. With this strategy, unnecessary urine culture could be reduced.

Conclusion: The prevalence of UTI among pregnant women admitted with premature uterine contractions was 4.9% and was not different between PTL/PPROM group and TPL group. Urinalysis with abnormal cell counts or significant bacteriuria could be a screening tool to reduce number of urine culture in women with TPL.

Keywords: Asymptomatic bacteriuria; urinalysis; urine culture; premature uterine contractions; pregnancy outcomes (Siriraj Med J 2023; 75: 699-706)

INTRODUCTION

Asymptomatic bacteriuria (ASB) is a significant bacterial infection of the urine without signs or symptoms of urinary infection. It is defined by the presence of one or more species of bacteria identified in the urine culture at a quantitative count of > 10^5 colony-forming units (CFU/ml).[1] Reported prevalence of ASB in pregnancy ranges from 2% to 7%[2] and may be higher in some conditions, such as diabetic pregnancies.[3] If pregnant women with ASB are not treated, up to 30% will develop acute pyelonephritis, which has been associated with low birth weight and preterm birth.[4] Therefore, once detected, active management with antibiotics is recommended.[5] Although early routine screening for and treatment of ASB in pregnancy are recommended in antenatal care guidelines,[6] the benefits and harm of screening and treatment are still questionable in low-risk singleton pregnancies.[7-9] Like most hospitals in Thailand, Siriraj

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Hospital does not perform screening for ASB during the antenatal period due to the low prevalence (2.3%) without a significant difference in prevalence by trimester.[9]

Preterm birth is an important cause of neonatal morbidity and mortality due to the immaturity/prematurity of the newborn various organ systems. Preterm birth rate at Siriraj Hospital was reported to be 9-14%.[10] Preterm birth usually is preceded by regular uterine contractions[11] or membrane rupture. Infection is one of the proposed mechanisms involved in this condition. Urinary tract infections (UTIs), genital tract infections, and periodontal diseases have been reported to be associated with spontaneous preterm labor.[12]

Premature uterine contraction is a common problem in pregnancy. As mentioned, the contractions can precede a preterm birth. On the other hand, the contractions can be a mere false alarm. Generally, regular uterine contractions with a cervical dilatation of ≥ 2 cm and ≥ 80% effacement have a high risk of labor progression, hence the condition is termed preterm labor (PTL). Condition of regular premature uterine contractions with less cervical changes is traditionally termed "threatened preterm labor" (TPL). However, with a subtle or borderline cervical change, it is difficult at the initial assessment to differentiate between early PTL and TPL. Further observation is needed to evaluate cervical progression. Another condition associated with preterm birth is preterm prelabor rupture of membranes (PPROM). It defines spontaneous membrane rupture before 37 completed weeks and before labor onset or cervical changes. With PPROM, risk of infection is increased along with time.

Management of pregnancies with either of the three conditions (PTL, PPROM, TPL) aims to delay delivery usually by tocolytics to avoid or reduce the risk of preterm birth unless/until there is a contraindication to do so. The women are admitted for evaluation and managed accordingly. Pregnancies with advanced PTL or PPROM are more likely than TPL to deliver in the same admission.

Guidelines suggested by the Royal Thai College of Obstetricians and Gynaecologists (RTCOG) for managing preterm labor recommend performing septic work-ups to determine if an infection is the cause of preterm labor. Urine analysis and urine culture are often used to diagnose UTIs, despite the absence of signs and symptoms with midstream urine culture (MUC) being the gold standard.[13] This is due to concern of ASB in these women.

At Siriraj Hospital, urinalysis is performed in women with premature uterine contractions on admission to detect UTI. Urine culture is also carried out simultaneously if feasible. This approach follows the RTCOG guidelines with an idea that UTI is a possible cause of premature uterine contractions or membrane rupture, which in turn may lead to preterm birth. If found, treating UTI may improve the pregnancy outcomes. However, previous studies could not demonstrate clear association between positive midstream urine culture (MUCs) in pregnancies with preterm labor, preterm delivery or pregnancy outcomes.[14] Furthermore, the rates of positive MUCs among women with preterm labor were reported to be 2.3% to 5% and the costs and benefits of performing MUCs were unclear.[9,14-16]

We aimed to determine the rate of UTI diagnosed by urinalysis and/or a positive urine culture in women admitted with premature uterine contractions. We carried out a study similar to the one previously performed in our institution.[15] However, in that study, only urine culture results had been considered. We added urinalysis into the diagnostic process to investigate whether urine culture number could be reduced or not. Furthermore, currently, the urine specimen would be collected by a single urinary catheterization instead of clean voided urine catch to reduce the risk of contamination especially from the vaginal discharge/fluids which often presented in larger amount than normal in cases with premature uterine contractions and/or PPROM. The common organisms involved and the association between the urine culture results and pregnancy outcomes were also evaluated.

MATERIALS AND METHODS

This retrospective study was performed at Siriraj Hospital, a tertiary care and teaching hospital in Bangkok, Thailand. The Institutional Review Board of the Faculty of Medicine Siriraj Hospital approved this study (COA no. Si 320/2018). The medical records of pregnant women admitted between January 2013 and December 2017 with an ICD-10 diagnosis code related to preterm with delivery (O60.1), preterm without delivery or threatened preterm labor (O60.0), and preterm prelabor rupture of membranes (O42.91) were reviewed. They received medications to inhibit labor, and were worked-up to determine the causes of premature uterine contractions. Pregnant women with an underlying renal disease or with a known urinary tract disease or with signs or symptoms of UTI from history taking and/or physical examination were excluded, as were cases with a contraindication for labor inhibition.

An "abnormal urinary analysis suggestive of UTI" was defined as a white blood cell count > 5/high-power field[17] or a red blood cell count > 5/high-power field without contamination and without crystal or casts.[18] As

we excluded women with preexisting urinary tract diseases, we assumed that abnormal urinalysis was associated with UTI. For urine culture, "positive growth" was defined as a bacterial count > 10^5 CFU/ml, whereas lower counts or positive growth of multiple organisms were more likely to be associated with contamination.[1] Since the women with symptoms of UTI had been excluded from the study, a positive growth in urine culture was also considered ASB.

Sample size was calculated based on the findings of Kiatsuda et al[19] that UTI or ASB were presented in 15.5% of women admitted with preterm labor or threatened preterm labor. With alpha of 0.05 and d= 0.015, the sample size needed was 2,237 women.

At the admission, an initial diagnosis was given according to the history taking and vaginal speculum and/or cervical examination as appropriate. Women were divided into two groups according to their diagnosis. As women with TPL were likely to be able to continue pregnancy and PTL/PPROM were likely to deliver in the same admission, they were allocated into either PTL/PPROM or TPL group. Patient characteristics, urinary results, and pregnancy outcomes were recorded on a case record form. Data analyses were performed using PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA). Descriptive data are presented as percentages, means, standard deviations (SDs), or medians with interquartile ranges (IQRs). Continuous variables were analyzed using Student's t-test, while categorical variables were examined with Pearson's Chi-square test or Fisher's exact test. A statistically significant difference was defined as a value < 0.05.

RESULTS

A total of 2,286 medical records were reviewed. Of these, simultaneous urinalysis and urine culture were available in 1,805 cases. There were 479 cases who had only urinalysis carried out. The remaining 2 cases had only culture result due to a mistake in specimen handling. As shown in Table 1, the mean maternal age at admission

TABLE 1. Basic characteristics of the study cohort.

Diagnosis at admission	n (%)	PTL/PPROM n (%)	TPL n (%)	*P* value
Total N = 2,286		810 (35.4)	1,476 (64.6)	
Age (years), mean = 29.1, (SD = 7.0)				
< 20	278 (12.2)	116 (14.3)	162 (11.0)	0.07
20 - 34	1,455 (63.6)	503 (62.1)	952 (64.5)	
≥ 35	553 (24.2)	191 (23.6)	362 (24.5)	
Gestational age at admission, mean = 31.3, (SD = 2.6)				
< 28	202 (8.8)	58 (7.2)	144 (9.8)	**< 0.001**
28- 31^{+6}	799 (35.0)	250 (30.9)	549 (37.2)	
32- 37	1,285 (56.2)	502 (62.0)	783 (50.3)	
Gestation				
Primigravida	1,102 (48.2)	392 (48.4)	710 (48.1)	0.89
Multigravida	1,184 (51.8)	418 (51.6)	766 (51.9)	
Parity				
Primipara	1,348 (59.0)	477 (58.9)	871 (59.0)	0.96
Multipara	938 (41.0)	333 (41.1)	605 (41.0)	
Prior preterm birth	156 (6.8)	63 (7.8)	93 (6.3)	0.11
Administration of dexamethasone for fetal lung maturity	2,122 (92.8)	731 (90.2)	1,391 (94.2)	**< 0.001**
complete	2,087 (91.29)	707 (87.28)	1,380 (93.50)	**< 0.001**
Side effects from inhibiting labor	903 (39.5)	264 (32.6)	639 (43.3)	**< 0.001**
Delivery in this admission	1,072 (46.89)	773 (95.43)	299 (20.26)	**< 0.001**

was 29 ± 7 years old and the mean gestational age was 31.3 ± 2.6 weeks. Approximately 60% of the women were primiparous. About 7% of the women had a history of a prior preterm birth. Table 2 shows that abnormal urinalysis suggestive of infection was presented in 94 cases (4.1% of those who had a urinalysis performed) and a positive urine culture was presented in 43 cases (2.4% of those who had urine culture performed). Among these two categories, there were 24 women who had both abnormal urinalysis and a positive urine culture. Therefore, altogether there were 113 women diagnosed with UTI by urinalysis and/or culture, comprising 4.9% of the total cohort.

As mentioned earlier, we divided women into two groups based on the initial diagnosis: PTL/PPROM group and TPL group. Approximately two-thirds of the women were diagnosed with TPL. The patient characteristics are summarized in Table 1. At the end, 20% of women with TPL delivered in the same admission, mostly from progression of labor. Ninety-five percent of women in PTL/PPROM group delivered in this admission. Women in this group who had not delivered were either referred to another hospital or discharged against advice. Length of stay of the total cohort was 8.8 ± 10.8 days, 9.3 ± 9 days and 8.5 ± 11.6 days in the total cohort, PTL/PPROM and TPL groups respectively.

Table 1 also shows that lower gestational age at admission were more prevalent in TPL group. This might be due to uterine contractions at such gestational age was likely to be a false alarm. The lower proportions of dexamethasone administration or side effects from inhibiting labor in the PTL/PPROM group were explained by the discontinuation of medications once the women delivered.

The urinary results of the cohort are presented in detail in Table 2. There were no statistically significant differences between the proportions of abnormal urinalysis (4.3% vs. 4.0%) or positive urine culture (1.7% vs. 2.7%) between PTL/PPROM group and TPL group. The most common organism identified in urine culture in both groups was *Escherichia coli*, presented in 40% and 75% in PTL/PPROM group and TPL group respectively.

TABLE 2. Urinary results of the study cohort.

Test		PTL/PPROM	TPL	
Urinalysis	**N = 2284, n (%)**	**N = 809, n (%)**	**N = 1475, n (%)**	***P* value**
Normal	2,190 (95.9)	774 (95.7)	1,416 (96.0)	0.71
Abnormal	94 (4.1)	35 (4.3)	59 (4.0)	
Mid-stream urine culture	**N = 1,807, n (%)**	**N = 600, n (%)**	**N = 1,207, n (%)**	
No growth	1,730 (95.7)	582 (97.0)	1,148 (95.1)	0.17
< 10^5 cfu/ml or contaminated	34 (1.9)	8 (1.3)	26 (2.2)	
Positive (>10^5 cfu/ml)	43 (2.4)	10 (1.7)	33 (2.7)	
Organisms in positive cultures				0.02
Escherichia coli	29 (67.4)	4 (40.0)	25 (75.8)	
Streptococcus agalactiae (Streptococcus group B)	2 (4.7)	2 (20.0)	0 (0.0)	
Enterococcus spp.	4 (9.3)	2 (20.0)	2 (6.1)	
Enterobacter spp.	2 (4.7)	0 (0.0)	2 (6.1)	
Klebsiella pneumoniae	2 (4.7)	0 (0.0)	2 (6.1)	
Citrobacter koseri	1 (2.3)	1 (10.0)	0 (0.0)	
Proteus mirabilis	2 (4.7)	0 (0.0)	2 (6.1)	
Staphylococcus saprophyticus	1 (2.3)	1 (10.0)	0 (0.0)	

Others various gastrointestinal bacteria were presented randomly in both groups. Remarkably, *Streptococcus agalactiae* (Streptococcus Group B; GBS) was found in 2 cases who were diagnosed with PPROM. Membrane rupture increases risk of urinary ascending infection from a rectovaginal GBS colonization.

Pregnancy outcomes were analyzed according to the urinalysis results in Table 3. Delivery rates in the studied admission were similar between women with abnormal and normal urinalysis and between women with positive and negative culture. Pregnancies with abnormal urinalysis had the gestational age at delivery and newborn birth weight greater than the corresponding values of the normal urinalysis group. This finding was despite the delivery rate and mode of the 2 groups being approximately the same. Unfortunately, when breaking into more details in gestational age or birth weight, there was no clear or consistent pattern to draw conclusion from. Other neonatal outcomes, such as the rates of birth asphyxia and neonatal intensive care unit (NICU) admission, were not significantly different.

Table 4 reveals pregnancy outcomes according to the urine culture results. Similar to urinalysis, delivery rates in the studied admission were similar between the women with a positive and a negative culture. On the other hand, pregnancies with a positive urine culture resulted in newborns with higher rates of extremely low birth weight (< 1,000 g) and NICU admission than cases with a negative urine culture. Even though the mode of delivery of these 2 groups was statistically similar, the cesarean section rate of the positive urine culture group was distinctly higher than that of the MUC-negative group (77.8% vs 52.5%).

From Tables 3 and 4, urine culture appears more meaningful than urinalysis. However, universal urine culture in cases with premature uterine contractions to identify the 2.4% positive rate would be costly. Based on the obtained data, we looked for a strategy to use the urinalysis as a screening tool to reduce the number of urine culture. Considering TPL comprising two-thirds of cases with premature uterine contractions, we concentrated on TPL group. In this group, simultaneous

TABLE 3. Pregnancy outcomes according to urinalysis results.

	Abnormal N = 94, n (%)	Normal N = 2,190, n (%)	*P* value
Delivery in this admission	52 (55.3)	1019 (46.5)	0.09
	N = 52	**N = 1019**	
Gestational age at delivery (weeks), mean (SD) 32.56 (SD = 0.074)	33.52 (2.236)	32.51 (2.418)	**0.003**
< 28	2 (3.8)	46 (4.5)	**0.048**
28- 31^{+6}	4 (7.7)	227 (22.3)	
32- 36^{+6}	46 (88.5)	727 (71.3)	
≥ 37	0 (0.0)	19 (1.9)	
Mode of delivery			
Normal delivery	23 (44.2)	466 (45.7)	0.89
Cesarean section	29 (55.8)	542 (53.2)	
FE/VE	0 (0.0)	5 (0.5)	
Assisted breech	0 (0.0)	6 (0.6)	
Birth weight (grams) 1,942.64 (SD = 566.20)	2,233.85(618.49)	1,927.62 (559.93)	**< 0.001**
< 1,000	2 (3.8)	42 (4.1)	0.002
1,000 - 1499	4 (7.7)	189 (18.5)	
1,500 - 2,499	28 (53.8)	632 (62.0)	
2500 or more	18 (34.6)	156 (15.3)	
Birth asphyxia[a]	3 (5.8)	98 (9.6)	0.35
NICU admission	12 (23.1)	345 (33.9)	0.11

Birth asphyxia[a] : Apgar score at 5 min after birth < 7

TABLE 4. Pregnancy outcomes according to results of urine culture.

N = 1,807	MUC + N = 43, n (%)	MUC - N = 1,764 n (%)	*P* value
Delivery in this admission	18 (41.9)	774 (43.9)	0.79
	N = 18	**N = 774**	
Gestational age at delivery (weeks), mean (SD) 32.56 (SD = 2.42)	31.72 (2.74)	32.28 (2.38)	0.33
< 28	3 (16.7)	39 (5.0)	0.16
28- 31^{+6}	3 (16.7)	187 (24.2)	
32- 36^{+6}	12 (66.7)	535 (69.1)	
≥ 37	0 (0.0)	13 (1.7)	
Mode of delivery			
Normal delivery	4 (22.2)	361 (46.6)	0.21
Cesarean section	14 (77.8)	406 (52.5)	
FE/ VE	0 (0.0)	4 (0.5)	
Breech assisting	0 (0.0)	3 (0.4)	
Birth weight (grams) 1,942.64 (SD = 566.20)	1,671.67 (664.30)	1,895.57 (549.15)	0.09
< 1,000	4 (22.2)	28 (3.6)	**0.001**
1,000 – 1,499	3 (16.7)	158 (20.4)	
1,500 - 2,499	9 (50.0)	481 (62.1)	
2,500 or more	2 (11.1)	107 (13.8)	
Birth asphyxia[a]	4 (22.2)	77 (9.9)	0.89
NICU admission	11 (61.1)	275 (35.5)	**0.03**

Birth asphyxia[a] : Apgar score at 5 min after birth < 7

urinalysis and culture were performed in 1,206 cases, urinalysis only in 269 cases and urine culture only in 1 case. Of the 1,206 cases who had both modalities of urine testing, the urine culture was positive in 33 cases. Within these 33 cases, 19 had an abnormal urinalysis based on WBC or RBC counts in the urine sediment. Thus, "abnormal urinalysis" using these criteria would detect only 57.6% of positive urine culture cases. Another marker from urinalysis was needed to improve sensitivity and the presence of bacteria in the sediment at the time of urinalysis was added into consideration. Urinalysis with abnormal cell count and/or presence of bacteria of ≥ 2+ was considered a positive screening. Urinalysis without significant cell count and significant presence of bacteria was considered negative. With this urinary screening criteria, a positive urine culture could be identified with the performance as shown in Table 5. The urine culture would have been performed in 78 cases (6.5%) with 90.9% sensitivity.

DISCUSSION

The overall prevalence of positive urine culture and abnormal urinalysis among pregnant women with premature uterine contractions was 2.4% and 4.1%, respectively. Considering in combination, UTI was present in 4.9%. The prevalence of abnormal urinalysis and positive urine culture were not significantly different between the PTL/PPROM and TPL groups. The most common organism identified was *Escherichia coli* in both groups. Newborns of women with positive urine culture had higher rates of extremely low birth weight (birth weight < 1,000 g) and admission to the NICU than newborns of women with negative urine culture.

Although ASB screening in early pregnancy is recommended as standard care, its benefits are still controversial. The reported prevalence of ASB among preterm labor or presumptive preterm labor groups has varied between studies.[14-16,20] The current investigation revealed a lower prevalence of positive urine culture

TABLE 5. Urinalysis as a screening tool for urine culture in TPL cases.

	Positive urine culture	Negative urine culture	Total
Positive urinalysis screening	30	48	78
Negative urinalysis screening	3	1,125	1,128
Total	33	1,173	1,206

Sensitivity: 90.9%; Specificity: 95.9%;
Negative predictive value: 99.7%; Positive predictive value: 38.5%
Positive urinalysis screening: Urinalysis with abnormal cell count and/or presence of bacteria of ≥ 2+
Negative urinalysis screening: Urinalysis without significant cell count and significant presence of bacteria (≤ 1+)

(2.4% vs 5%) among pregnant women admitted with premature uterine contractions than an older study at our institute.[15] More recent research at our hospital in 2015 revealed a comparable prevalence among pregnancies in any trimester without premature uterine contraction.[9] The prevalence might have decreased due to different urine collection techniques, which changed from voluntary urination to clean urinary catheterization.

The most common organism for positive urinary culture in the present investigation was *Escherichia coli*, which was similar to the findings of other investigations.[9,15,20,21] The current work also found 2 women with *Streptococcus agalactiae* (Group B *Streptococcus*; GBS), both presented with PPROM which might have increased the risk of urinary infection from the rectovaginal colonization of GBS. Antenatal screening of GBS colonization and the use of an appropriate intrapartum antibiotic prophylaxis should be considered to prevent newborn infections.[22]

This study showed that abnormal urinalysis and positive urine culture were not associated with delivery rate in that particular admission. This evidence agrees with other work in which an MUC was not recommended as a routine laboratory test in pregnancy with preterm labor without clinical indications.[14] However, newborns of pregnancies with positive MUCs were related to poor neonatal outcomes, such as risk of extremely low birth weight and NICU admission.[7,8]

Our study revealed a rather low prevalence of abnormal urinalysis (4.1%) and positive urine culture (2.4%) in pregnancies with premature uterine contractions. We propose a strategy to identify those who need a urine culture in women diagnosed with TPL instead of universal culture. Urinalysis is first performed and the results are used for contemplating urine culture. The cases with abnormal WBC or RBC counts, or cases a bacteria rating of ≥ 2+ should proceed to urine culture, while those with normal cell counts and lower rate of bacteria in the sediment should not. With this strategy, only 6.5% of cases with TPL would need urinary culture with 90.9% sensitivity. This would save cost, time and manpower considerably. The evidence from this study can be used to guide the routine ordering of appropriate laboratory tests.

This study assessed the benefit of simultaneous urinalysis and urine culture in women with premature uterine contractions with a large number of subjects. Moreover, a strategy to reduce number of unnecessary urine culture in TPL cases has been proposed. However, this retrospective study was unable to demonstrate a causal relationship. Besides, selection bias from incomplete screening might have affected the results as urine culture was performed in 79% of the total cohort.

In conclusion, routine urinalysis and urine culture in women admitted with premature uterine contractions did not predict whether the pregnancy could be continued or not. However, adverse neonatal outcomes were more common in pregnancies with positive urine culture. Urinalysis result could be used to identify women with TPL who should have a urine culture to reduce unnecessary culture.

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Conflict of interest

None declared.

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Efficacy of Music Therapy and *Zingiber officinale* Roscoe Aromatherapy for Reducing Pain during the First Stage of Labor: A Randomized Controlled Trial

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ABSTRACT

Objective: To study the pain-reducing effect of music therapy and aromatherapy with ginger essential oil (GEO; Zingiber officinale Roscoe) in the first stage of labor.

Materials and Methods: This randomized controlled trial was conducted from May 2022 to March 2023 in the delivery room of Thammasat University Hospital in Thailand. Participants were nulliparous pregnant women who came with actual labor pain and cervical dilation of 3 cm. They were divided into three groups: control, music, and aromatherapy. The control group received intrapartum care according to hospital guidelines, while participants in the music group listened to a "Musical Journey through Pregnancy" music playlist, and the aromatherapy group inhaled GEO. A visual analog scale was used for pain assessment every 2 hours. Interventions and pain assessment continued until the end of the first stage of labor or until cesarean section was indicated.

Results: Three hundred pregnant women were recruited. The mean age of the participants was 27.7 years old, and no difference in BMI among the three groups. Participants in the music and aromatherapy group had statistically significantly less labor pain than participants in the control group when cervical dilation was between 4 and 7 cm (6,1±0.7, 1.9±0.7, 2.6±0.4 when cervical dilation was 4-5 cm and 8.0±0.7, 2.8±0.4, 3.6±0.3 when cervical dilation was 6-7 cm in the control, music, and aromatherapy groups, respectively ($p < 0.001$). However, at cervical dilation of 8-10 cm, there was no difference among the three groups regarding labor pain. Both intervention groups had significantly shorter labor time and less estimated blood loss during vaginal delivery than the control group ($p < 0.001$).

Conclusion: Music and aromatherapy decreased labor pain, labor time, and estimated blood loss compared to the control group.

Keywords: Labor pain; music therapy; aromatherapy (Siriraj Med J 2023; 75: 707-712)

INTRODUCTION

Labor pain is one of the most painful experiences in a woman's life. It results from contraction of the uterus, dilation of the cervix, and dilation of the adjacent pelvic organs. This pain has significant physiological effects on the health of the mother and fetus.[1] Therefore, its minimization in the intrapartum period is considered crucial. Conventional methods can reduce pain during labor[2] but also have disadvantages, such as decreased consciousness during labor, respiratory distress in the

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newborn[3], slowing of the fetal heart rate[1], maternal respiratory suppression, nausea, vomiting, dizziness, and drowsiness.[1,4] For these reasons, non-pharmacological methods such as music therapy, yoga, relaxation, and other methods are becoming more popular worldwide.[5]

Several studies have shown that music therapy can reduce anxiety, stress, and pain in pregnant women[5-10] by stimulating the brain to produce dopamine and endogenous opioids.[8] In addition, music therapy has been found to improve heart rate variability in pregnant women.[9] Other studies have shown that geranium, frankincense, lavender, jasmine, and rose essential oils can relieve anxiety and labor pain.[11,12] Ginger essential oil (GEO; Zingiber officinale Roscoe) is an essential oil extracted from the ginger plant and abundant in Southeast Asia. It is currently available worldwide and is used to relieve pain in various organs through various mechanisms.[13] However, studies on labor pain after inhalation have not yet been conducted. These two alternative therapies are simple, inexpensive, and have no serious side effects. Therefore, we aim to investigate the efficacy of music therapy and GEO aromatherapy for pain relief in the first stage of labor.

MATERIALS AND METHODS

This randomized controlled trial was conducted among pregnant women admitted to the delivery room of Thammasat University Hospital from May 2022 to March 2023. A flowchart of the study according to the Consolidated Standards of Reporting Trials (CONSORT) is shown in Fig 1. The inclusion criteria were nulliparous, pregnant women aged 15 to 45 years old, singleton pregnancy, gestational age of ≥ 37 weeks, initial cervical dilation of 3 cm, use of oxytocin for labor augmentation, and ability to understand and communicate Thai language. Exclusion criteria were women who had an indication for cesarean section since admission, did not have a cephalic presentation, and had schizophrenia, anosmia, deafness, or chronic diseases that can exacerbate back pain or Covid-19 infection. Women who experienced adverse effects such as nausea and dizziness after inhaling GEO disliked the smell of GEO after using it for more than 10 minutes, experienced headaches or pain in their ears when listening to music for more than an hour, disliked the music, or were uncomfortable using headphones, or removed headphones for more than an hour were excluded from the study. Women who received opioid or regional anesthesia during delivery and women who wanted to end their participation in the study were also later excluded from the study.

After admission to the delivery room, research assistants presented and explained the research objectives to potential candidates who met the inclusion criteria. If they decided to participate in the study, their consent was obtained. Baseline data and clinical symptoms were recorded on a data collection form. Participants were

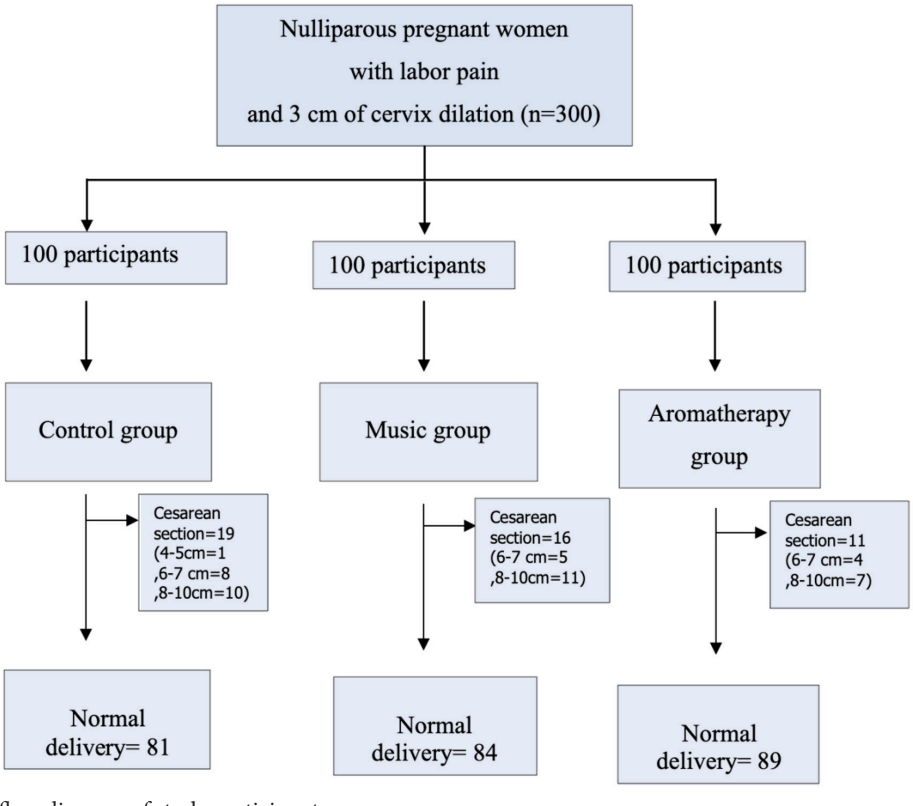

Fig 1. The CONSORT flow diagram of study participants

randomly assigned to three experimental groups: the control group, the music group, and the GEO aromatherapy group. The consecutively numbered assignments were sealed in opaque envelopes. Each group was placed in a different room. The control group received routine treatment, while the music group listened to a collection of music entitled "Musical Journey through Pregnancy"[10] through headphones, consisting of 8 songs that were uplifting, gentle, and natural sounds. The aromatherapy group inhaled the GEO reed diffuser placed next to the bed, and participants in all groups were in different rooms. All three groups received interventions and were assessed for pain every 2 hours using a visual analog scale (VAS) until the end of the first stage of labor or cesarean section was indicated. Satisfaction was assessed after the end of labor. The pain scale was divided into mild (pain score 0-3), moderate (pain score 4-6), and severe (pain score 7-10) pain groups for further and more precise information.

Statistical analysis

The sample size was calculated using the formula with two independent groups, and the mean values of 3.82 and 4.39 were used from a previous study.[14] With an alpha-type error rate of 1% (two-sided) and statistical power of 80% (one-sided), the estimated sample size per group was 93. With an expected sample loss of 5%, the final size was adjusted to 100 cases per group, resulting in a total of 300 participants in the study.

Descriptive statistics were reported as mean, percentage, frequency, and standard deviation. Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, IL, USA) was used for data analysis. One-way analysis ANOVA was performed, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 300 nulliparous pregnant women were randomized equally to the control, music, and aromatherapy groups, with no participant withdrawal. The average age was 27.7 years old. The gestational age of each group was approximately 38 weeks. About half (145/300) of participants had a normal BMI. Almost all participants had no underlying diseases. There were no significant differences in participants' characteristics between groups, as shown in Table 1.

Our study showed no differences in baseline VAS scores among the three groups. The mean VAS at cervical dilation of 4-5 cm were 6.1, 1.9, 2.6, and at the dilation of 6-7 cm, were 8.0, 2.8, and 3.6 for the control, music, and aromatherapy groups, respectively. The VAS score for cervical dilatations of 4-5 cm and 6-7 cm was significantly lower in both intervention groups than in the control group (p < 0.001), and the VAS score in the music group

TABLE 1. Demographic of the participants (100 case each).

Demographic	Control	Music	Aroma	*P*-value*
Age (years), mean ± SD	28.0±4.7	28.0±5.6	27.07±4.9	0.303
Gestational age (weeks), mean ± SD	38.5±1.1	38.1±3.2	38.1±1.0	0.344
BMI, n (%)				0.803
Underweight	28 (28)	29 (29)	30 (30)	
Normal	45 (45)	49 (49)	51 (51)	
Overweight	19 (19)	16 (16)	16 (16)	
Obese	8 (8)	6 (6)	3 (3)	
Gestational weight gain (kg), mean ± SD	13.1±4.4	12.9±4.9	12.0±5.1	0.254
Underlying disease, n (%)	2 (2)	1 (1)	4 (4)	0.359
Pregnancy complication, n (%)				0.409
GDM	11 (11)	10 (10)	9 (9)	
PIH	7 (7)	2 (2)	3 (3)	
Others	3 (3)	6 (6)	4 (4)	

*; Analysis of variance p-value <0.05 indicates statistically significant

Abbreviations: BMI: Body mass index, GDM; Gestational diabetes mellitus, PIH; Pregnancy induce hypertension

was significantly lower than in the aromatherapy group ($p < 0.001$).

In addition, the VAS score was further subdivided into severity levels. With cervical dilation of 4-5 cm, all participants in both intervention groups had mild pain. In contrast, most participants in the control group had moderate pain. At cervical dilation of 6-7 cm, all participants in the music group had mild pain; three-fourths of participants in the aromatherapy group also had mild pain, while most participants in the control group had severe pain, as shown in Table 2.

In both intervention groups, the first and second stages of labor were significantly shorter than in the control group. There were no differences in the rate of cesarean deliveries among the three groups, the most common indication being (15, 16, and 11 cases in the control, music, and aromatherapy groups, respectively, in that order). Another indication that led to cesarean delivery in the control group was abnormal fetal heart rate. Moreover, the estimated blood loss (EBL) for vaginal delivery was significantly lower in both intervention groups than in the control group ($p < 0.001$). However, no difference was found for cesarean delivery ($p = 0.305$). The mean birth weight was 3.0-3.1 kg in all groups. Almost all neonates in all groups had standard Apgar scores in the first and fifth minutes of life, except for one case in the control group with an Apgar score of 5.6 in the first and fifth minutes of life, subsequently. All pregnant women in both intervention groups reported high satisfaction with a score of 7-10 out of a total of 10 points, while about four-fifths of participants in the control group were only moderately satisfied with a score of 4-6 out of a total of 10 points.

DISCUSSION

The management of labor pain is one of the significant issues in obstetrics, for which various methods of relief are being explored. Previous studies showed that noninvasive complementary and adjunctive strategies, namely music therapy and aromatherapy, significantly reduce initial labor pain[7,15,19] (and other clinically relevant outcomes.[10,15] In addition, many studies have found that both interventions can reduce anxiety in stressful situations.[5,6,9,11,16,20] Currently, no study uses GEO inhalation and compares GEO aromatherapy with music therapy for pain relief in the first stage of labor. Therefore, we propose these two therapies for nulliparous pregnant women to treat labor pain in the first stage of labor.

TABLE 2. Pain score and severity score of the participants during various cervical dilatation.

Cervical dilate (cm)	Control	Music	Aroma	*P*-value*
3, mean ± SD	1.3±0.5	1.4±0.5	1.4±0.5	0.338
4-5, mean ± SD	6.1±0.7§	1.9±0.7¶	2.6±0.4	<0.001
Pain severity score, n (%)				<0.001
Mild	0	99 (100)	92 (100)	
Moderate	79 (80.6)	0 (0)	0 (0)	
Severe	19 (19.4)	0 (0)	0 (0)	
6-7, mean ± SD	8.0±0.7§	2.8±0.4¶	3.6±0.3	<0.001
Pain severity score, n (%)				<0.001
Mild	0 (0)	95 (100)	62 (72.9)	
Moderate	3 (3.3)	0 (0)	23 (27.1)	
Severe	87 (96.7)	0 (0)	0 (0)	
8-10, mean ± SD	9.1±0.3	9.0±0.8	9.0±0.7	0.859
Pain severity score, n (%)				
Mild	0 (0)	0 (0)	0 (0)	
Moderate	0 (0)	0 (0)	0 (0)	
Severe	91 (100)	95 (100)	96 (100)	

*; Analysis of variance p-value <0.05 indicates statistically significant, §; Significant difference from the other 2 group, ¶; Significant difference from aroma group, Pain score 0-3; mild, 4-6; moderate, 7-10; severe pain

TABLE 3. Obstetrics data of the participants (100 case each).

	Control	Music	Aroma	*P*-value*
Time labor (min)†				
1st stage	513.0±178.7§	381.8±145.8	383.5±160.8	<0.001
2nd stage	23.1±14.7§	15.0±10.4	15.3±10.1	<0.001
C/D‡	19(19)	16(16)	11(11)	0.284
V/DEBL (ml)†	347.0±212.2§	144.1±100.7	150.0±85.3	<0.001
BW (kg)†	3.1±0.4	3.1±0.4	3.0 ±0.4	0.095
Apgar ≥7‡				0.367
1 min	99 (99)	100 (100)	100 (100)	
5 min	99 (99)	100 (100)	100 (100)	
Satisfaction‡				<0.001
Moderate (4-6)	81 (81)	0 (0)	0 (0)	
Excellent (7-10)	19 (19)	100 (100)	100 (100)	

*; Analysis of variance p-value <0.05 indicates statistically significant, †; mean± standard deviation, §; Significant difference from the other 2 group, ‡; n (%)

Abbreviations: C/D; cesarean delivery, V/DEBL; vaginal delivery estimate blood loss, BW; birth weight

In our study, participants were distributed among the research groups, and there were no significant differences in demographic characteristics. Most participants in the three groups had no underlying diseases, and there were no differences in cervical dilation, baseline pain scores, or augmentation rates.

Our study showed that participants in both intervention groups had significantly less labor pain than the control group when cervical dilation was 4-7 cm. Based on these results, we can assume that both music and aromatherapy are effective in reducing pain in the early active phase of the first stage of labor, which is consistent with previous studies in both the music[7,17,18] and aromatherapy groups[14,16,19] In addition, our study found that music therapy was more effective than GEO aromatherapy in reducing labor pain in the early active phase. The mechanism for pain relief in both interventions is unclear. However, music and aromatherapy may stimulate brain substances that serve as natural analgesics. However, in the late active phase of labor (cervical dilation of 8-10 cm), no significant difference in the severity of labor pain was observed among the three groups in our study. A lower focus on both interventions can explain this, as pain is more intense in the late active phase of labor.

Furthermore, we could hypothesize that music therapy is beneficial in shortening the duration of the first and second stages of labor, which is consistent with Gonzalez's study.[10] Although this result contradicts a previous study by Guo[15], which found that music can prolong the first stage of labor, these different results may be explained by differences in the type of music and the duration of music listening.

Additionally, GEO aromatherapy has significantly reduced the duration of the first and second stages of labor. This finding contrasts the results reported by Tanvisut[14] and Yazdkhasti.[19] It could be due to differences in the type of aromatherapy, the duration during which the participants were exposed to the fragrances, and the diffuser used.

Our study also showed that both intervention groups had a statistically significant reduction in EBL during vaginal delivery, consistent with the results reported by Guo.[15] However, the mechanisms responsible for these results remained unexplained. Both intervention groups showed higher satisfaction levels than the control group, which may be due to the calming effect of these interventions, which helped to reduce stress during the waiting period.

Our study is the first to report the effectiveness of music therapy in reducing the time of the second stage of labor. In addition, our research reports for the first time that the scent of GEO can effectively reduce labor pain during the early active phase of the first stage of labor, the duration of labor, and EBL for vaginal birth.

Our results could be a milestone for future studies. At the same time, we are aware of the study's limitations, such as the lack of blindness to interventions and the fact that it is a single-center design.

CONCLUSION

This study showed that music and GEO aromatherapy effectively reduced labor pain in the early active phase of the first stage of labor, with music therapy being an effective therapy. In addition, music and GEO aromatherapy reduced the duration of the first and second phases of labor, estimated blood loss during vaginal delivery, and had higher satisfaction levels among participants in both intervention groups. This study recommends both therapies as a cost-effective and complementary approach for treating initial labor pain in the delivery room.

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Conflict of interest

Authors declare no conflict of interest for this article.

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Heart Rate Variability and Baroreflex Sensitivity: Factors and Reference Ranges

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ABSTRACT

Objective: Heart rate variability (HRV) and baroreflex sensitivity (BRS) are influenced by various internal and external factors, making it necessary to establish universal reference values. We aimed to identify independent factors affecting short-term HRV parameters and BRS, as well as determine appropriate reference ranges, which are lacking in Asian populations.

Materials and Methods: A total of 117 healthy Thai participants (aged 20-72 years; final n=117) were recruited based on strict criteria, including normal medical history, physical examination (ascertained by a physician), and normal blood profile. Spontaneous 5-minute HRV parameters (time and frequency domains) and spontaneous cross-correlation BRS were measured.

Results: Age and resting heart rate (HR) are independently and inversely correlated with BRS and all HRV parameters, except LFnu (normalized low-frequency component) and LF/HF ratio (ratio of low- to high-frequency component). Sex differences were observed only in LF, which was higher in men. However, multiple regression analysis showed that sex did not significantly contribute as an independent variable to either HRV or BRS. Remarkably, BRS exhibited moderate to strong correlations with all HRV values, indicating its prominent role in influencing HRV and surpassing the impact of age.

Conclusion: Age and resting HR were identified as independent factors influencing 5-minute HRV and BRS. Our findings suggest that decreased baroreflex function associated with aging may contribute to reduced HRV among the elderly. Furthermore, we established reference ranges for each 5-minute HRV parameter and BRS, categorized by age group (20-39, 40-59, and ≥60 years old). These reference values offer valuable clinical insights, particularly for Asian populations where such normative ranges were previously unavailable.

Keywords: Heart rate variability; baroreflex sensitivity; reference values; healthy subjects; cardiovascular autonomic assessment (Siriraj Med J 2023; 75: 713-724)

INTRODUCTION

Heart rate variability (HRV) and baroreflex sensitivity (BRS) are quantitative markers that represent cardiovascular autonomic functions.[1-3] HRV measures the oscillation of interbeat (RR) intervals, which reflects the central sympathetic and parasympathetic modulation of the heart.[4] BRS refers to the relationship between changes in systolic blood pressure (SBP) and corresponding RR intervals. It is widely accepted that hemodynamic parameters and derivatives, including HRV and BRS, are influenced by various internal and external factors, such as age, sex, ethnicity, recording procedures, surrounding

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temperature and environment.[1,2,5-11] Consequently, it is necessary to establish reference ranges for HRV and BRS that are specific to each laboratory to ensure meaningful interpretation, and facilitate inter-laboratory comparisons.[12] However, there are considerable variations in HRV and BRS reference values, even among Asian individuals[10,13-15], likely due to disparities in recording duration, analysis methods, and other factors.[5,12,16]

HRV and BRS have been increasingly employed in the clinical setting, mostly in clinical trials, e.g., as risk assessment tools in coronary artery diseases.[17,18] HRV is sometimes used as an additional investigation in patients with atypical postural orthostatic tachycardia syndrome or POTS.[19] Moreover, their recording practicality have made both HRV and BRS widely used for other purposes besides clinical applications. For example, HRV is used as an objective stress measurement in e-sport players[20] and training monitoring parameters in sports science.[21] This popularity, however, resulted in a huge variation in procedure and outcome, leading to difficulties in interpretation, particularly when comparing among studies without reference values.

Resting, short-term assessments of HRV (5 minutes) and BRS (10 minutes) are noninvasive and practical for clinical investigations.[1,2,12,17-19,22] However, standardized 5-minute HRV reference values for Asian adults are currently lacking age stratification[13] or fail to demonstrate age dependence.[20] While a few studies in Thailand have compared HRV and BRS between patients and controls or different groups[23-25], normal values for the Thai population have not yet been established, limiting the clinical use in the region. Our aim was to determine factors that influence short-term HRV parameters and BRS, and to establish reference values for healthy Thai adults.

MATERIALS AND METHODS

This study was approved by the Siriraj Institutional Review Board (COA no. Si 679/2012).

Participants

We enrolled healthy Thais, aged 20-80 years, from Bangkok. All participants provided written informed consent and met the following criteria: normal BMI (18.5-22.9 kg/m^2)[26], and blood profile within the last six months, including complete blood count (CBC), fasting blood glucose (FBG), blood urea nitrogen (BUN), creatinine, liver function tests, and lipid profile: triglyceride (TG) <200 mg/dL and total cholesterol <200 mg/dL, or ≥200mg/dL with calculated LDL (cal-LDL) <160 mg/dL, and HDL >50 mg/dL (women) or >40 mg/dL (men). The exclusion criteria was as follows: diabetes mellitus; cardiovascular diseases (e.g., hypertension); abnormal electrocardiogram (ECG); pulmonary diseases, including obstructive sleep apnea; psychiatric diseases; use of drugs that affect the autonomic nervous system (ANS), with the exception of statins and baby aspirin; current smokers or individuals who had quit smoking <1 year; heavy alcohol drinkers (>2 standard drinks per day); individuals with occupations that affect the ANS, such as security guards and athletes; acute illness; and pregnancy. All female participants were assessed outside their menstruation period.

Data collection

Participants avoided alcoholic beverages for ≥48 hours, and caffeinated beverages, vitamins, herbs, and intense exercise for ≥12 hours. Upon arrival at the Cardiovascular Autonomic Function Laboratory, Department of Physiology, participants underwent an interview and a comprehensive physical examination conducted by a physician. Recorded data comprised participant demographics, including sex, age, BMI, exercise habits, alcohol consumption, menstruation, resting blood pressure (BP), and heart rate (HR) using an automatic sphygmomanometer.

The autonomic assessment took place in a quiet room, with a temperature of 23-24°C, humidity between 50-60%, and commenced at least ≥2 hours after the last meal. Noninvasive continuous hemodynamic parameters were measured using the Finometer® Pro device with an ECG module (lead II) and analyzed with the BeatScope® Easy program (Finapres Medical System BV, Amsterdam, The Netherlands), at a sampling rate of 200 Hz.

The protocol began with a 10-minute period of rest in a supine position, with system calibrations performed between the 6th and 10th minute. Subsequently, continuous measurements of blood pressure (BP) and ECG were recorded for 12 minutes, during which participants remained awake, quiet, and relaxed.

Data and statistical analysis

HRV analysis was performed using LabChart®7Pro software (ADInstrument, Castle Hill, Australia). A 5-minute segment of stable ECG data without, ectopic beats was manually selected to derive 11 time- and frequency-domain HRV parameters and BRS, as shown in Table 2.

Statistical analyses were performed using SPSS software (IBM Corporation, New York, USA). Data normality was assessed using the Kolmogorov-Smirnov test. Results were reported as mean±SD, with additional median and interquartile range (P_{25}-P_{75}) provided for non-normally distributed data. For comparisons between

groups, the unpaired t-test or one-way ANOVA with *post hoc* Tukey's test was used for normally distributed data, while the Mann-Whitney U test or Kruskal-Wallis test with *post hoc* Dunn's test was applied for non-normally distributed data, as appropriate. A P value <0.05 was considered statistically significant.

Pearson correlation analysis was utilized to determine the linear correlation between continuous data and HRV parameters or BRS. Correlation coefficients (r) falling within the range $0.36 \leq |r| < 0.68$ or $|r| \geq 0.68$ were regarded as indicating moderate or strong correlations, respectively.[27] Factors that exhibited significant differences in parameters between groups or significant correlations with HRV or BRS values were further included in a stepwise multiple regression analysis to identify independent determinants. Lastly, reference values for each parameter were determined based on percentile values and categorized as normal, borderline, or abnormal as described in Table 5.

RESULTS

Participant general characteristics

Of the 144 initially interviewed healthy participants, 27 individuals were excluded due to abnormal blood profiles or physical examination findings. The general characteristics of the remaining 117 participants (44 men and 73 women) are summarized in Table 1. The mean age was similar between men and women. Men exhibited higher BMI, BP, and respiratory rate (RespR), but had significantly lower resting HR. All blood profile data were within normal limits, consistent with the inclusion criteria (data not shown). The participants were divided into three age groups: 20-39, 40-59, and 60-79 years (n=56, 40, and 21, respectively). In the two younger age groups, the average ages did not differ significantly between sexes, while in the oldest group, women were older than men (average age, women vs. men, 64.41 vs. 60.50 years, n=17 vs. 4, respectively) (Supplemental Materials, Table S.1).

Comparisons of HRV and BRS among independent groups

The comparison of HRV parameters and BRS among different age groups is presented in Table 2. Most parameters showed a declining trend with age, except for LFnu, HFnu, and LF/HF, which were not dependent on age. The 40-59 age group generally did not differ significantly from the 60-79 age group, except for SDNN, Total power, and LF, which were higher in the 40-59 age group. Interestingly, we observed no significant differences between sexes in all parameters except for LF, which was higher in men (Table S.2).

We also examined HRV and BRS differences in relation to other characteristics. However, no significant differences were found when caffeine drinkers vs. non-caffeine drinkers, non-heavy alcohol drinkers vs. non-alcohol drinkers, regular exercise vs. sedentary individuals,

TABLE 1. Participants' general characteristics.

Characteristics	Men (n = 44)	Women (n = 73)	P value
Age (year)	39.00 ± 12.82	44.11 ± 14.94	ns[a]
BMI (kg/m^2)	21.29 ± 1.21, 21.65 (20.22 - 22.32)	20.75 ± 1.09	0.0127[b]
SBP (mmHg)	118.16 ± 10.50	109.89 ± 11.77, 108.00 (101.00 - 115.50)	0.0002[b]
DBP (mmHg)	73.39 ± 8.10	69.01 ± 8.69	0.0079[a]
MAP (mmHg)	88.31 ± 8.19	82.64 ± 8.97	0.0009[a]
HR (/min)	67.25 ± 8.20	72.10 ± 9.75, 72.00 (66.00 - 76.50)	0.0053[b]
RespR (/min)	15.98 ± 9.69, 13.00 (12.00 - 16.00)	15.38 ± 2.14, 16.00 (14.00 - 16.00)	0.0040[b]

Data are mean±SD. Medians (P_{25} - P_{75}) are additionally shown for non-normally distributed data. [a]Unpaired t-test (normally distributed data); [b]Mann-Whitney U test (non-normally distributed data); ns, not statistically significant or $P \geq 0.05$.

TABLE 2. Comparison of HRV parameters and BRS among age groups.

Parameters	20-39 years (n=56)	40-59 years (n=40)	60-79 years (n=21)	*P* value
HRV				
Time domain parameters				
SDNN (ms)	56.98 ± 28.43, 46.51 (38.04 – 70.12)	46.42 ± 18.22, 42.31 (34.29 – 56.85)	32.34 ± 13.69*,#	<0.0001[b]
SDSD (ms)	50.88 ± 30.92, 41.07 (33.40 – 64.85)	31.76 ± 16.69*	22.78 ± 11.59*, 19.15 (15.98 – 26.16)	<0.0001[b]
RMSSD (ms)	50.80 ± 30.86, 41.01 (33.36 – 64.74)	31.71 ± 16.66* 19.12 (15.95 – 26.12)	22.74 ± 11.56*,	<0.0001[b]
pNN50 (%)	26.43 ± 20.55, 21.54(10.60 – 41.89)	10.76 ± 13.96*, 4.77(1.58 – 17.98)	5.82 ± 9.20*, 2.11(0.80 – 6.02)	<0.0001[b]
Frequency domain parameters				
Total power (ms^2)	4083.40 ± 4348.02, 2414.42 (1235.23 - 4844.84)	2366.20 ± 2036.57, 1671.50 (1302.74 - 2742.20)	1215.93 ± 1336.86*,#, 900.07(487.06 - 1325.66)	<0.0001[b]
LF (ms^2)	1173.82 ± 1509.87, 681.23 (307.11 - 1398.26)	495.05 ± 385.00*, 373.62(254.98 - 729.60)	270.82 ± 309.08*,#, 184.38(104.17 - 304.04)	<0.0001[b]
LFnu	42.93 ± 15.51	56.73 ± 15.84*	50.90 ± 19.91	0.0436[a]
HF (ms^2)	1491.10 ± 2040.50, 763.31 (418.14 - 1551.51)	444.77 ± 571.81*, 286.37 (167.51 - 535.86)	226.89 ± 225.34*, 151.41 (97.97 - 212.00)	<0.0001[b]
HFnu	51.12 ± 16.14	40.00 ± 15.71*	44.95 ± 18.67	0.0058[a]
LF/HF	1.09 ± 0.78, 0.86 (0.45 - 1.52)	1.89 ± 1.77*, 1.22 (0.79 - 2.21)	1.62 ± 1.45, 1.42 (0.67 - 2.00)	<0.0289[b]
BRS (ms/mmHg)	19.15 ± 9.87, 15.72 (12.35 - 22.89)	11.20 ± 5.15*, 10.37 (8.68 - 13.08)	8.21 ± 2.58*	<0.0001[b]

Data are mean±SD. Medians (P_{25} - P_{75}) are additionally shown for non-normally distributed data. [a]One-way ANOVA followed by *post hoc*; [b]Kruskal-Wallis test followed by *post hoc* Dunn's test (non-normally distributed data); *,#Significant difference compared to age groups *20-39 years or #40-59 years, respectively; ns, not statistically significant or $P \geq 0.05$.

Abbreviations: SDNN, standard deviation of the NN interval (NN stands for normal-to-normal RR interval); RMSSD, the root mean square of differences between adjacent NN intervals; SDSD, standard deviation of differences between adjacent NN intervals; pNN50, proportion of NN50 to total NN intervals (NN50 stands for number of adjacent NN interval pairs with a difference greater than 50 ms); VLF, very low frequency (≤ 0.4 Hz); LF, low frequency (0.04-0.15 Hz); HF, high frequency (0.15-0.4 Hz); LFnu, normalized unit of LF; HFnu, normalized unit of HF.

women in the follicular vs. the luteal phase of the menstrual cycle, and morning vs. afternoon assessment time (Table S.3-S.7).

Correlation analysis

Correlation analysis was conducted between each HRV parameter or BRS and all factors, including hemodynamic and blood profile measures. Age showed a moderate negative correlation with all absolute HRV parameters (excluding LFnu, HFnu, and LF/HF) and BRS. Additionally, a weak negative correlation was observed between age and HFnu, while a weak positive correlation was found between age and LFnu or LF/HF. Resting HR, but not BP, exhibited a moderate inverse correlation with three time-domain HRV indices, namely SDSD, RMSSD, and pNN50. Furthermore, BRS displayed a stronger negative correlation with SBP than resting HR (Table 3). Other factors not shown in the table, including blood profile data, either showed no significant correlation with HRV parameters or BRS ($P \geq 0.05$), or displayed significant but weak correlations ($P < 0.05$, $|r| < 0.36$).

Stepwise multiple regression

To determine independent influences on each HRV or BRS parameter, stepwise multiple regression analysis was conducted. All factors with any significant correlation or differences between groups were included in the analysis, resulting in a total of 22 parameters: sex (men=0, women=1), age, BMI, weight, height, SBP, DBP, MAP, HR, RespR, ambient temperature, humidity, FBG,

TABLE 3. Correlations between HRV parameters or BRS vs age, BMI, resting BP, and HR.

Parameters	Age	BMI	SBP	DBP	MAP	HR
HRV						
Time domain parameters						
SDNN	***r* = -0.45** ****	ns	*r* = -0.19 *	ns	ns	*r* = -0.34 **
SDSD	***r* = -0.50** ****	ns	*r* = -0.29 **	ns	*r* = -0.20 *	***r* = -0.37** ****
RMSSD	***r* = -0.50** ****	ns	*r* = -0.29 **	ns	*r* = -0.20 *	***r* = -0.37** ****
pNN50	***r* = -0.53** ****	ns	*r* = -0.30 **	ns	*r* = -0.22 *	***r* = -0.40** ****
Frequency domain parameters						
Total power	***r* = -0.38** ****	ns	ns	ns	ns	*r* = -0.32 **
LF	***r* = -0.37** ****	ns	ns	ns	ns	*r* = -0.23 *
LFnu	*r* = 0.21 *	*r* = 0.34 ***	*r* = 0.22 *	ns	*r* = 0.18 *	ns
HF	***r* = -0.40** ****		*r* = -0.24 **	ns	ns	*r* = -0.26 **
HFnu	*r* = -0.26 **	*r* = -0.26 **	*r* = -0.26 **	*r* = -0.19 *	*r* = -0.24 *	*r* = -0.19 *
LF/HF	*r* = 0.23 *	*r* = 0.22 *	*r* = 0.24 **	*r* = 0.21 *	*r* = 0.23 *	ns
BRS	***r* = -0.59** ****	ns	***r* = -0.42** ****	ns	*r* = -0.33 ****	*r* = -0.27 ****

r, Pearson's correlation coefficient; ns, not statistically significant or $P \geq 0.05$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$. Significant correlations with $|r| > 0.36$ are shown in bold type.

TG, cal-LDL, ALT, Hb, Hct, RBC, WBC, neutrophil (N), and eosinophil (%E). Table 4 displays the multiple linear equations and their adjusted coefficient of determination (Adj. R2) for each HRV and BRS value. The independent variables in each equation are presented in order of their contribution size to the regression model. Age was the main contributing variable for all time-domain HRV parameters, Total power, LF, HF, and BRS, followed by resting HR. Interestingly, sex did not emerge as a significant variable in any of the equations, suggesting that any differences in HRV parameters between sexes may be an epiphenomenon. It is worth noting that none of the adjusted R^2 exceeded 0.50, indicating that the factors included in the study accounted for less than 50% of the variance in each parameter. It is possible that other factors not considered in our study may play a role.

Relationship between HRV parameters and BRS

BRS exhibited a strong positive correlation with all time-domain HRV parameters. It also displayed positive correlations with most frequency-domain parameters, except for LFnu and LF/HF ratio, which showed an inverse correlation (Table S.8). Among the HRV parameters, RMSSD (r=0.86), SDSD (r=0.86), pNN50 (r=0.85), and HF (r=0.80), which are associated with parasympathetic activity, showed the strong positive correlations with BRS. LF exhibited a moderate correlation (r=0.59). Given

TABLE 4. Stepwise multiple regression results for HRV parameters and BRS.

	Regression equation				Adj. R^2
HRV					
Time domain parameters					
SDNN	= 159.929 *(90.992)*	- 0.836 Age *(40.820)*	- 1.170 HR *(24.619)*		0.335
SDSD	= 170.202 *(100.290)*	- 0.985 Age *(55.108)*	- 1.381 HR *(33.375)*		0.407
RMSSD	= 169.864 *(100.261)*	- 0.984 Age *(55.129)*	- 1.377 HR *(33.344)*		0.407
pNN50	= 117.848 *(104.949)*	- 0.748 Age *(69.339)*	- 1.065 HR *(43.356)*		0.468
Frequency domain parameters					
Total power	= 17092.348 (47.557)	- 99.590 Age *(26.480)*	- 153.131 HR (19.307)		0.258
LF	= 4487.946 *(27.694)*	- 31.256 Age *(22.031)*	- 36.928 HR *(9.484)*		0.190
LFnu	= -97.336 *(9.417)*	+ 5.091 BMI *(14.765)*	+ 0.337 SBP *(5.916)*		0.143
HF	= 6645.337 *(34.556)*	- 46.026 Age *(27.188)*	- 58.678 HR *(13.627)*		0.236
HFnu	= 190.121 *(35.468)*	- 4.392 BMI *(11.759)*	- 0.604 HR *(10.511)*	- 0.303 Age *(8.997)*	0.177
LF/HF	= 2.063 *(9.345)*	+ 0.013 TG *(12.495)*	- 0.248 WBC *(7.015)*		0.139
BRS	= 53.412 *(94.140)*	- 0.377 Age *(76.833)*	- 0.356 HR *(21.172)*		0.436

Adj. R^2, adjusted coefficient of determination; italicized numbers in parentheses are F-to-remove of the parameter immediately above.

these robust associations, we conducted a reanalysis by incorporating HRV and BRS into the stepwise multiple regression calculation for each other (Table S.9A and S.9B). The inclusion of both variables resulted in improved predictive power (Adj. R^2) in every model. Interestingly, BRS emerged as the most influential variable for predicting all HRV parameters, replacing the variance explained by age (Table S.9A). Furthermore, RMSSD, a vagal HRV parameter, contributed the most to the BRS value (Table S.9B).

Age-specific reference values of HRV parameters and BRS (Table 5)

The reference values for HRV parameters and BRS were categorized by age group, except for LFnu and LF/HF, which were age-independent (Table 4). These values were organized into five intervals based on percentile, as described in the Materials and Methods section. As expected, the age-dependent parameters were highest in the youngest age group.

DISCUSSION

In this study, we examined short-term HRV (5 minutes) and spontaneous cross-correlation BRS in 117 healthy Thai volunteers (44 men and 73 women, 20-72 years). Our findings revealed that BRS and most HRV parameters, namely, SDNN, SDSD, RMSSD, pNN50, Total power, LF, HF, and HFnu, were negatively and independently correlated with age and resting HR. However, factors such as sex, most blood profile components, caffeine intake, alcohol drinking, exercise, menstrual phase, and assessment time did not show any significant associations with HRV parameters and BRS.

Major determinants of HRV and BRS are age and resting heart rate.

Age and resting heart rate are major determinants of HRV parameters and BRS in healthy subjects. The negative correlation between age and all parameters, except for LFnu and LF/HF, was observed in both the correlation study and stepwise multiple analysis (Table 3 and 4). These results are consistent with several studies reporting a decline in HRV and BRS with age in healthy participants[5,14,28-31] with our comparison of HRV parameters among age groups (Table 2). Our rigorous inclusion and exclusion criteria ensured the selection of a homogeneous pool of healthy subjects, indicating that the negative correlation with age represents a normal aging process rather than a pathology.[32] The absence of an age association with LFnu and LF/HF was supported by the stepwise multiple regression results (Table 4), aligning with the findings of Remaekers *et al.*[33] Furthermore, the differences were primarily observed between the youngest group (20-39 years) and the two older groups. The average or median values of HRV and BRS in the age group 40-59 and ≥60 were generally similar, especially parasympathetic-associated HRV parameters: RMSSD, pNN50, and HF. The two older groups only differed significantly in SDNN, Total power, and LF (Table 2). Although this discrepancy could be attributed to the small sample size in the oldest age group, a study has shown that older subjects (60-77) did not differ significantly from the oldest middle-age group (40-59), which supports our results.[28] Possible explanations include a faster decline in HRV values with age in younger individuals[32] and a more linear correlation between sympathetic modulation, global autonomic regulation HRV (LF and SDNN, respectively) and age compared to parasympathetic modulation.[14,34]

Another significant independent factor affecting HRV and BRS, as observed in our data, is resting HR. While this factor is less frequently reported[6,33,35], we found a negative correlation between resting HR and most HRV parameters and BRS, similar to the age effect but of smaller magnitude (Table S.9A and S.9B). Our results are generally in agreement with Ramaekers *et al.*[33], who reported negative correlations between HR and SDNN, SDSD, pNN50, RMSSD, Total power, LF, and HF, except for LFnu and LF/HF ratio. Since resting HR is associated with cardiac autonomic tone, while HRV parameters are more related to cardiac autonomic regulation[4], the negative correlation suggests reduced cardiac autonomic modulation at higher autonomic tone. Alternatively, it may reflect limited variability at narrower RR intervals.[36]

BMI did not show a significant association with most HRV parameters and BRS in our study, and it only weakly influenced LFnu and HFnu. In contrast, a study by Vallejo *et al.*[37] in 30 females (21-35 years; BMI ranging from <19 to >30kg/m^2) found that both age and BMI significantly affected HRV. The discrepancy may be attributed to the narrower range of BMI in our healthy participants (18.5-22.9kg/m^2), or the fact that the other study did not include resting HR in their analysis (which could be a determinant variable of BMI).

HRV parameters and BRS are probably not sex dependent.

Most HRV parameters and BRS were not significantly different between men and women, except for significantly higher LF in men (Table S.2). Additionally, sex did not appear in any of the stepwise multiple regression equations (Table 4), indicating that sex was not an independent factor determining HRV parameters and BRS in healthy

TABLE 5. Normal, borderline, and abnormal values for HRV parameters and BRS.

Parameters		Age 20-39 years (n = 56)	40-59 years (n = 40)	> 60 years (n = 21)
SDNN (ms)				
	A_H	≥ 122.62	≥ 84.38	≥ 65.70
	B_H	91.87 - 122.61	68.28 - 84.37	43.17 - 65.69
	Normal	**27.54 - 91.86**	**26.89 - 68.27**	**20.75 - 43.16**
	B_L	22.01 - 27.53	20.48 - 26.88	17.49 - 20.74
	A_L	≤ 22.00	≤ 20.47	≤ 17.48
SDSD (ms)				
	A_H	≥ 144.20	≥ 66.57	≥ 50.14
	B_H	86.01 - 144.19	47.27 - 66.56	41.48 - 50.13
	Normal	**21.56 - 86.00**	**15.04 - 47.26**	**14.11 - 41.47**
	B_L	15.87 - 21.55	10.94 - 15.03	10.33 - 14.10
	A_L	≤ 15.86	≤ 10.93	≤ 10.32
RMSSD (ms)				
	A_H	≥ 143.91	≥ 66.44	≥ 50.04
	B_H	85.86 - 143.90	47.20 - 66.43	41.42 - 50.03
	Normal	**21.53 - 85.85**	**15.02 - 47.19**	**14.08 - 41.41**
	B_L	15.85 - 21.52	10.92 - 15.01	10.32 - 14.07
	A_L	≤ 15.84	≤ 10.91	≤ 10.31
pNN50 (%)				
	A_H	≥ 69.21	≥ 44.07	≥ 28.81
	B_H	56.11 - 69.20	27.41 - 44.06	22.74 - 28.80
	Normal	**1.86 - 56.10**	**0.49 - 27.40**	**0 - 22.73**
	B_L	0.67 - 1.85	0 - 0.48	0
	A_L	≤ 0.66	*	*
Total power (ms^2)				
	A_H	≥ 16429.82	≥ 7089.93	≥ 4396.11
	B_H	8407.85 - 16429.81	5220.90 - 7089.92	2308.46 - 4396.10
	Normal	**681.03 - 8407.84**	**760.36 - 5220.89**	**403.65 -2308.45**
	B_L	474.08 - 681.02	398.73 - 760.35	333.98 - 403.64
	A_L	≤ 474.07	≤ 398.72	≤ 333.97
LF (ms^2)				
	A_H	≥ 4492.49	≥ 1574.98	≥ 1122.30
	B_H	3006.39 - 4492.48	996.83 - 1574.97	416.35 - 1122.29
	Normal	142.66 - 3006.38	149.08 - 996.82	73.44 - 416.34
	B_L	74.83 - 142.65	78.57 - 149.07	59.40 - 73.43
	A_L	≤ 74.82	≤ 78.56	≤ 59.39
LFnu				
	A_H		≥ 82.24	
	B_H		71.53 - 82.23	
	Normal		**23.29 - 71.52**	
	B_L		17.34 - 23.28	
	A_L		≤ 17.33	

TABLE 5. Normal, borderline, and abnormal values for HRV parameters and BRS. (Continue)

Parameters		Age 20-39 years (n = 56)	40-59 years (n = 40)	> 60 years (n = 21)
HF (ms²)				
	A_H	≥ 6835.77	≥1734.42	≥ 816.01
	B_H	3284.54 - 6835.76	868.83 - 1734.41	461.89 - 816.00
	Normal	**218.61 - 3284.53**	**92.57 - 868.82**	**78.78 - 461.88**
	B_L	57.65 - 218.60	36.49 - 92.56	55.68 - 78.77
	A_L	≤ 57.64	≤ 36.48	≤ 55.67
HFnu				
	A_H	≥ 77.99	≥ 67.40	≥ 80.39
	B_H	72.25 - 77.98	55.73 - 67.39	72.84 - 80.38
	Normal	**31.41 - 72.24**	**18.41 - 55.72**	**25.10 - 72.83**
	B_L	24.50 - 31.40	12.22 - 18.40	16.72 - 25.09
	A_L	≤ 24.49	≤ 12.21	≤ 16.71
LF/HF				
	A_H		≥ 6.47	
	B_H		2.88 - 6.46	
	Normal		**0.34 - 2.87**	
	B_L		0.22 - 0.33	
	A_L		≤ 0.21	
BRS (ms/mmHg)				
	A_H	≥ 45.19	≥ 19.96	≥ 12.44
	B_H	34.08 - 45.18	14.90 - 19.95	10.95 - 12.43
	Normal	**10.52 - 34.07**	**5.34 - 14.89**	**4.87 - 10.94**
	B_L	7.08 - 10.51	4.70 - 5.33	4.37 - 4.86
	A_L	≤ 7.07	≤ 4.69	≤ 4.36

Normal, P_{10}-P_{90}; borderline low (B_L) ≥ $P_{2.5}$ to < P_{10}; borderline high (B_H) > P_{90} to ≤ $P_{97.5}$; abnormally low (A_L) < $P_{2.5}$; abnormally high (AH) > $P_{97.5}$; *, not defined.

subjects. The difference in LF between men and women could be attributed to the negative correlation between LF and resting HR (Table 3), as men tend to have lower resting HR than women (Table 1). Although many reports have described sex differences in HRV, especially in young adults[12,13], most of these studies did not utilize multiple regression analysis in their investigations.

BRS is highly correlated with HRV.

BRS has been found to have a positive correlation with HRV in both normotensive and hypertensive subjects. It is also the most important determinant in predicting HRV in multiple regression analysis[38,39], which is consistent with our findings. Although BRS and HRV both reflect cardiovascular autonomic functions, they represent different aspects and are not redundant. Therefore, it is reasonable to consider their correlations.[17]

The parasympathetic components of HRV, such as RMSSD, SDSD, pNN50, and HF, exhibited higher correlations with BRS compared to sympathetic or global autonomic components like LF, SDNN, and Total power (Table S.8). These distinct correlations support the notion that activation and deactivation of sympathetic or parasympathetic control during blood pressure fluctuation are not mirror images. While the SA node is controlled by both parasympathetic and sympathetic cardiac fibers, the vagal response is much faster, leading to immediate changes in RR intervals in response to blood pressure fluctuations.[2] Furthermore, it is important to note that our study, despite the 'baroreflex

sensitivity' name, specifically focused on the cardiovagal branch of the baroreflex arc, as we derived responses from RR intervals, while excluding changes in sympathetic vasomotor tone. Thus, it is not surprising that our results align with other studies showing a high correlation between BRS and cardiac vagal control.[40]

The high correlations observed between HRV parameters and BRS can provide insights into the mechanisms underlying reduced HRV with aging (Table 4). Studies associating HR and BP oscillations have suggested a close relationship between HRV and baroreceptor function.[41,42] In our study, we attempted to integrate these two observations by including BRS in the multiple regression analysis to predict each HRV parameter and vice versa. The inclusion of BRS replaced all HRV variance previously accounted for by age and emerged as the most influential factor, exhibiting the highest proportion of squared semi-partial correlation for each HRV parameter (Table S.9A). In other words, the age-related decline in HRV can also be explained by the reduced d BRS. Therefore, a decline in baroreceptor or baroreflex function may contribute to the diminished HRV observed in older individuals.

Age-specific reference values of HRV parameters and BRS

The present study presents reference values for 5-minute HRV and cross-correlation BRS in a sample of healthy Thai individuals (Table 5). We identified age and resting HR as independent factors influencing HRV and BRS, while sex did not show a significant association. Therefore, we categorized the reference values into three age groups without considering sex stratification. The reference values were presented based on percentiles since most of the HRV and BRS data exhibited nonparametric distribution.

While many studies in Asian populations defined normal ranges for short-term HRV in terms of mean ± SD, with or without age specification[13,14,43], the only other study reporting age-adjusted reference values in percentile in Asian individuals (in Brazil) was conducted by Dantas *et al.*[44] Comparing our reference values in in the frequency domain with the Asian Brazilian data, we observed higher values. These differences could be attributed to variations in analytical methods or environmental factors among the study subjects.

We provided age-adjusted reference values for BRS using the spontaneous cross-correlation sequence method, which has been suggested to be more reliable than the sequential method.[22] To the best of our knowledge, our reference values for cross-correlation BRS may be the only ones reported for an Asian population. However, Tang *et al.*[15] recently published spectral BRS reference values for a Chinese population. When compared to the ATRAMI study[17], which reported BRS values in post-myocardial infarction patients, our lower limit for abnormal BRS (AL) was higher than the cut-point associated with increased cardiac mortality (3ms/mmHg) in those patients. This disparity can be explained by the ATRAMI study inclusion of non-healthy subjects, with a higher average age (57 years), and the use of phenylephrine injection to determine BRS.

Limitations

Our sampling rate for BP and ECG signal provided by the Finometer® Pro device was limited to 200 Hz maximum[45], which was lower than the Task Force's recommendation at 250-500 Hz.1 However, there is evidence that 200 Hz is acceptable for HRV and BRS analysis, especially for healthy subjects.[46]

We were unable to provide reference values based on age and resting HR, even though they are both independent variables in HRV and BRS regression equations, due to limited sample size, especially in the oldest age group. Another limitation of our study is that the reference values are specific to the spontaneous 5-minute HRV recording and cross-correlation BRS method. While these methods are valuable and practical in clinical settings, further research is needed to establish reference values for 24-hour HRV recording and spectral analysis BRS, specifically for the Thai population.

CONCLUSION

Our study provides age-dependent reference values for spontaneous 5-minute HRV and cross-correlation BRS in healthy Thai adults, aged 20-72, along with an understanding of the factors influencing them. We found that HRV parameters, except LFnu and LF/HF ratio, as well as BRS, were independently and negatively correlated with age and resting HR, while sex did not show a significant association. Moreover, our results suggest that the decline in HRV with age may be partially attributed to age-related reductions in baroreflex function. The reference values and insights gained from our data analysis will serve as a foundation for the interpretation of HRV and BRS values in autonomic research and clinical practice.

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Conflict of interest statement

None to declare.

Abbreviations: %E, percent eosinophil; Adj. R2, adjusted coefficient of determination; AH, abnormally high; AL, abnormally low; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANOVA, analysis of variance; BH, borderline high; BL, borderline low; BMI, body mass index; BP, blood pressure; bpm, beat per minute; BRS, baroreflex sensitivity; BUN, blood urea nitrogen; cal-LDL, calculated low-density lipoprotein cholesterol; CBC, complete blood count; DBP, diastolic blood pressure; dl, deciliter; ECG, electrocardiogram; FBG, fasting blood glucose; h, hour; Hb, hemoglobin; Hct, hematocrit; HDL, high-density lipoprotein cholesterol; HF, high frequency (0.15-0.4 Hz); HFnu, high frequency power in normalized unit; HR, heart rate; HRV, heart rate variability; Hz, Hertz; kg, kilogram; LF, low frequency (0.04-0.15 Hz); LFnu, low frequency power in normalized units; m2, square meter; MAP, mean arterial pressure; mg, milligram; mmHg, millimeter of mercury; ms, millisecond; N, neutrophil count; NN interval, the interval between two successive normal R waves; NN50, number of adjacent NN interval pairs with a difference greater than 50 ms; pNN50, proportion of NN50 to total NN intervals; r, Pearson's correlation coefficient; R2, coefficient of determination; RBC, red blood cell count; RespR, respiratory rate; RMSSD, root mean square of differences between adjacent NN intervals; RR interval, the interval between two successive R waves; SA node, sinoatrial node; SBP, systolic blood pressure; SD, standard deviation; SDNN, standard deviation of the NN interval; SDSD, standard deviation of differences between adjacent NN intervals; TG, triglyceride; VLF, very low frequency (≤0.4 Hz); WBC, white blood cell count

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Cost-Effectiveness Analysis of Long-acting Injectable Once-monthly of Aripiprazole Compared with Long-acting Injectable Once-monthly Paliperidone Palmitate for the Treatment of Stable Schizophrenia Patients in Thailand

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ABSTRACT

Objective: Long-acting injectable (LAI)-aripiprazole and LAI-paliperidone palmitate are both second-generation antipsychotics that have been introduced to increase drug compliance in patients. These attributes are expected to enhance drug compliance, particularly in stable patients. The previous studies demonstrated that the efficacy of LAI-aripiprazole and LAI-paliperidone palmitate is controversial. Nevertheless, the costs of treatments and adverse events of both LAI-aripiprazole and LAI-paliperidone palmitate are unlikeness. As there had been no previous cost-effectiveness studies comparing the use of LAI-aripiprazole and LAI-paliperidone palmitate in Thailand, this study was carried out to investigate the matter.

Materials and Methods: This study analysed the cost-effectiveness of LAI-aripiprazole compared with LAI-paliperidone palmitate in the treatment of stable schizophrenia, by using the Markov model from a societal perspective.

Results: The total cost of treatment with LAI-aripiprazole and LAI-paliperidone palmitate was 1,334,919.05 baht and 1,329,818.79 baht, respectively, while the quality-adjusted life years (QALYs) were both 16.35 years. Life-year of the treatment with LAI-aripiprazole and LAI-paliperidone was 24.27 years and 24.25 years, respectively. The cost-effectiveness ratios (CER) of the treatment with LAI-aripiprazole and LAI-paliperidone palmitate were 81,652.85 baht/QALY gained and 81,330.94 baht/QALY gained, respectively.

Conclusion: In Thailand, the treatment of stable schizophrenia with LAI-aripiprazole was shown to provide similar benefits to LAI-paliperidone palmitate in terms of QALYs, despite being more costly. Comparatively, LAI-aripiprazole exhibited better clinical efficacy and led to a longer average life expectancy than LAI-paliperidone. Treatment with LAI-aripiprazole may be dominant strategy, especially with a 2% reduction in drug cost. The results could contribute to appropriate decision-making by policymakers.

Keywords: Aripiprazole; cost-effectiveness; long-acting injectable antipsychotics; paliperidone; stable schizophrenia patients (Siriraj Med J 2023; 75: 725-735)

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INTRODUCTION

Schizophrenia is a chronic mental illness affecting cognition, emotion, and behaviour. Over 24 million people around the world are impacted by the illness. With about 5.5 million sufferers, China has the highest rate of schizophrenia in the entire globe.[1] Schizophrenia incidence rates range from 8 to 43 per 100,000 individuals.[2,3] It is a considerable economic and social burden worldwide since the afflicted patients are hardly able to work. Nowadays, schizophrenia is one of the 25 leading causes of disability worldwide4 and one of the top ten causes of Disability-Adjusted Life Years (DALYs).[4,5] In Thailand, approximately 8.8 per 1000 of the population suffer from schizophrenia, and was the eighth or ninth leading cause of years lived with disability.[6] It also consumed a large amount of annual cost of treatment (i.e., estimated to be THB 87,000 (USD 2,600) per person or THB 31,000 million (USD 925 million) for the entire schizophrenic population in Thailand.[7]

Treatment of schizophrenia includes both pharmacological and non-pharmacological therapies.[8] The goal of treatment is to improve the patient's quality of life by reducing the symptoms and preventing relapse of patients. For example, conventional and atypical antipsychotics are commonly used for the treatment of schizophrenia[9], but conventional antipsychotics produces extrapyramidal symptoms (EPS) while atypical antipsychotics have been reported as metabolic adverse events, e.g., weight gain, hyperlipidemia, and hyperglycemia. Both adverse events have affected patients' compliance.[9,10] Therefore, for some patients, even if they control their symptoms and are discharged from the hospital, 30-40% of discharged patients relapse within 1-2 years.[11] Patient compliance is one of the important factors associated with relapse.[12-15] Non-adherent patients were approximately three times more likely to be hospitalized in a given year, according to a study conducted in the United States.[16]

Recently, long-acting injection (LAI) antipsychotics have been suggested to be used[17], particularly in the prevention of relapse for non-compliant patients, according to the most evidence-based guidelines for the maintenance treatment of schizophrenia.[18] LAIs are recommended as a first-line treatment.[18] Thai clinical guidelines[19] have been updated to include LAI first-generation antipsychotics (e.g., Fluphenazine decanoate and Haloperidol decanoate) as well as LAI second-generation antipsychotics (e.g., LAI-aripiprazole and LAI-paliperidone palmitate) to improve medication compliance in stable schizophrenia patients. Currently, LAI second-generation have been used more than first-generation antipsychotics because they have lower EPS side effects.[19]

LAI-aripiprazole and LAI-paliperidone are both second-generation antipsychotics that have been introduced to increase drug compliance[20] since they are LAIs and administered once a month. These attributes are expected to enhance drug compliance, particularly for stable patients who are not inpatients. However, they have different pharmacological mechanisms.[21] Aripiprazole is a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at 5HT2A receptors while Paliperidone is an antagonist at D2 and 5HT2A receptors. The different mechanisms may contribute to different effectiveness and tolerability.[22] The previous comparative studies[23,24] demonstrated that the efficacy of LAI-aripiprazole and LAI-paliperidone is controversial. Nevertheless, the costs of treatments and adverse events of both LAI-aripiprazole and LAI-paliperidone are unlikeness.[22,23] Utilizing the economic evaluation as a tool for selecting the optimal LAI strategy would be reasonable.

Previously, no cost-effectiveness studies have been carried out that compared the use of LAI-aripiprazole and LAI-paliperidone palmitate in Thailand from the societal perspective. A cost-effectiveness study is crucial in order to evaluate and compare these antipsychotics. Therefore, the cost-effectiveness of LAI-aripiprazole and LAI-paliperidone palmitate was investigated in this study.

MATERIALS AND METHODS

Study design

This study was health economic evaluation using a Markov model to compare the cost-effectiveness of LAI-aripiprazole with LAI- Paliperidone palmitate for the treatment of stable schizophrenia. The analysis was carried out using cost-effectiveness ratios (CER) and presented humanistic outcomes in Quality-Adjusted Life Years (QALYs). The perspective of this study was societal. Future costs and utilities were discounted at 3 percent per year.[24] This study has been reviewed and approved by the Human Research Ethics Committee of Silpakorn University (COE 65.1007-165)

Treatments

This study compared monthly dosages of LAI-aripiprazole 400 mg and LAI-paliperidone palmitate 156 mg (equivalent dose of Paliperidone 100 mg).[25-28] Patients with schizophrenia who did not respond to LAI-aripiprazole or LAI-paliperidone palmitate treatment were switched to 300 mg per day of clozapine[29], which is the only antipsychotic medicine approved by the FDA for treatment-resistant schizophrenia.[30]

Decision model

The decision model was developed based on previously studies of antipsychotics used in the treatment of schizophrenia patients.[31] A Markov model was used to perform decision analysis through Microsoft Excel 2020. The model and assumptions were validated for the disease sequence to ensure its appropriateness for the treatment of stable schizophrenia in Thailand by three psychiatrists.

The model comprises three main health states including remission under the first antipsychotic, relapse, and death, see Fig 1. A 'death state' is a state where a patient dies for any reason. 'Relapse state' denotes patients who have suffered an exacerbation of their condition and hospital admission, due to non-compliance or the inefficacy of LAI-aripiprazole or LAI-paliperidone. Patients who are not in the death or relapse state are in the 'remission state' Transition probabilities and health state utilities were reviewed and derived from published literature.

The model simulated stable schizophrenia patients over the period of their lifetime. Patients were assigned 400 mg LAI-aripiprazole every 4 weeks or 156 mg LAI-paliperidone palmitate (equivalent dose of Paliperidone 100 mg) every 4 weeks. All stable patients under first LAI antipsychotic entered the model in the 'remission state' at the beginning of the simulation. It was assumed that the health transition state cycle was 4 weeks. At the end of each cycle, mortality rate, the probability of relapse status, and any adverse events occurrence (i.e., akathisia, dystonia, parkinsonism, dyskinesia, diabetes mellitus, hyperprolactinemia, and weight gain) were assessed for each group of LAI antipsychotics until all the patients died. Patients with 'remission state' were not changed health state if they did not experience any adverse events. Patients who did not respond to LAI due to inefficacy of the treatment were switched to 300 mg per day of clozapine as a second antipsychotic. Patients who experienced relapse due to one of two conditions: (1) Non-compliance with, or inefficacy of LAI-aripiprazole or LAI-paliperidone palmitate, or (2) Relapse from remission with taking clozapine were moved to the relapse state and were switched to 300 mg per day of clozapine as a second antipsychotic. Assumingly, patients who switched to clozapine would continue receiving it until the end of the study. Patients in all states could be moved to the death state throughout the study period according to the probability of death.

Assumptions of the model

1. Patients did not withdraw from the treatment during the study and remained until the end of study.

2. Patients who received LAI-aripiprazole were initially administered with a single injection of 400 mg aripiprazole followed by 20 mg of oral aripiprazole for the first 14 days (i.e., concurrent with the first dose of LAI). This was followed by monthly injections of 400 mg aripiprazole thereafter.

3. Patients who received LAI-paliperidone palmitate were initially administered with injection of 400 mg (equivalent dose of Paliperidone 250 mg) in the first month. This was followed by monthly injections of 156 mg paliperidone palmitate (equivalent dose of Paliperidone 100 mg) thereafter.

4. Patients administered with LAI-aripiprazole or LAI-paliperidone could potentially experience common adverse drug reactions, i.e., akathisia, dystonia, parkinsonism, dyskinesia, diabetes mellitus, hyperprolactinemia, and weight gain.

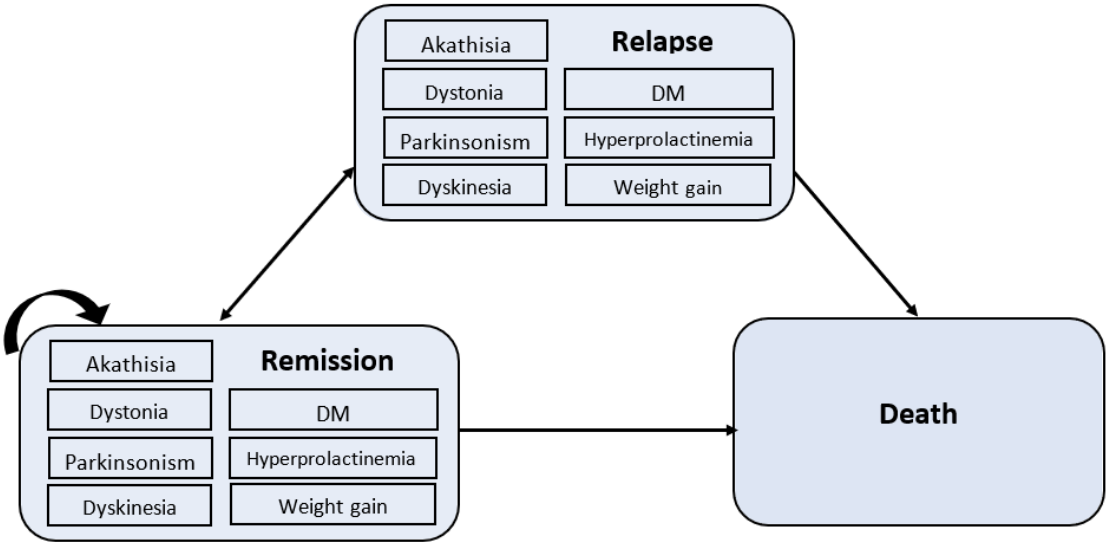

Fig 1. Markov model structure of Schizophrenia disorder.

5. Hyperprolactinemia was defined as a serum prolactin level greater than or equal to 25 ng/mL and patients who experienced hyperprolactinemia were switched to clozapine 300 mg per day (or 100 mg three times per day).

6. Weight gain was defined as body weight increased to greater than or equal to 7 percent of basal body weight, and patients who experienced weight gain were provided with counselling.

7. Diabetes mellitus was defined as plasma glucose levels greater than or equal to 200 mg/dl or fasting blood glucose levels greater than or equal to 126 mg/dl which could be reversed when treated with 1,000 mg of metformin daily to control diabetes.

8. Patients who had akathisia were treated with 40 mg per day of propranolol.

9. Patients who had dyskinesia were switched to clozapine 300 mg per day (or 100 mg three times per day).

10. Patients who had dystonia were assumed to be suffering from only mild dystonia and were treated with 6 mg of trihexyphenidyl per day (or 2 mg three times per day).

11. Patients who had parkinsonism were treated with 6 mg of trihexyphenidyl per day (or 2 mg three times per day).

12. Patients who switched to clozapine and experienced a form of agranulocytosis, which is defined as ANC <500 cells per microlith, received 300 micrograms of filgrastim daily, for 7 days.

13. Patients who did not respond to LAI due to inefficacy were switched to 300 mg per day of clozapine as a second antipsychotic.

14. Patients in a relapsed state of health relapsed due to one of two conditions: (1) Non-compliance with, or inefficacy of LAI-aripiprazole or LAI-paliperidone palmitate, or (2) Relapse from remission while taking clozapine.

15. Patients had not received other antipsychotics or other co-interventions.

16. Patients in all health states who received LAI-aripiprazole or LAI-paliperidone palmitate could be moved to the death state based on the normal mortality rate of the Thai population.[32] In the case of patients who received clozapine, the mortality rate was based on the mortality rate of schizophrenia patients.[33]

Time horizon

A Markov model was developed to imitate the treatment of adult schizophrenia patients over a lifetime period from the age of 18 until death with a life expectancy of not more than 75.7 years.[34] A cycle length of 4 weeks was considered appropriate to capture both the clinical treatment and associated events such as relapses and adverse drug reactions from a survey of treatment in Thailand.[7]

Probability of clinical outcomes

A systematic search was conducted in Medline, SCOPUS and Cochrane databases. The keywords were "schizophrenia, Paliperidone, and Aripiprazole", with filtering by randomized controlled trial, meta-analysis, systematic reviews, full text and English published literature. Two reviewers independently reviewed abstracts, and articles sequentially to select studies for data abstraction based on the study eligibility criteria. All searched literature was evaluated and given a JADAD score. All probabilities were converted into risks over 4 weeks because of the cycle length and are shown in Table 1.

Studies were identified as eligible for inclusion if they were published as full papers and in the English language. All transition probabilities were obtained from studies involving schizophrenia patients who have used LAI-aripiprazole or LAI-paliperidone. The utility of health states was obtained from studies involving Thai schizophrenia patients who used LAI-aripiprazole or LAI-paliperidone with/or without any adverse events. Where search results were inconclusive, the study proceeded as follows: (i) involving schizophrenia patients controlled by antipsychotics drug and whether they had side effects, or (ii) other patients who had utility of health state and side effects, or (iii) utility was retrieved from international studies due to the limited data in Thailand. Articles were excluded from the review if they met any of the following criteria: (i) non-full text papers, (ii) editorials and opinions, letters, research protocols, conference abstracts, duplicate reports of the same study, and notes and books.

Costs

All costs are expressed in Thai baht and are shown in Table 1. Drug treatment costs were derived from the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health, Thailand.[35]

All drug costs (i.e., LAI-aripiprazole, LAI-paliperidone palmitate, Clozapine, metformin, propranolol, trihexyphenidyl, and filgrastim) were obtained from the drug's median price in Thailand. Costs of meals, nursing care costs, and laboratory costs including tests for FBS, haemoglobin A1c, serum prolactin, and complete blood counts were obtained from the mean cost per unit of secondary care by standard cost lists for health

TABLE 1. All parameters used in the Markov model.

Parameters	Distribution	Mean ± SE	References
Probabilities			
Transition probabilities			
LAI-aripiprazole			
Relapse from Inefficacy	Beta	0.02260 ± 0.00797	25-28
Relapse from non-compliance	Beta	0.00355 ± 0.00859	26
Probabilities of adverse drug reaction			
Hyperprolactinemia	Beta	0.00000 ± 0.00000	28
Akathisia	Beta	0.00229 ± 0.00217	22, 23, 25
Dyskinesia	Beta	0.00057 ± 0.00146	23
Dystonia	Beta	0.00132 ± 0.00185	22, 23
Parkinsonism	Beta	0.00356 ± 0.00302	22, 23
Weight gain	Beta	0.00277 ± 0.00172	22, 23, 28, 43, 44
Diabetes	Beta	0.00015 ± 0.00124	43
LAI-paliperidone palmitate			
Relapse from Inefficacy	Beta	0.02497 ± 0.00880	26-28
Relapse from non-compliance	Beta	0.00378 ± 0.00575	26
Probabilities of adverse drug reaction			
Hyperprolactinemia	Beta	0.00002 ± 0.00000	25
Akathisia	Beta	0.00169 ± 0.00213	22, 23, 25
Dyskinesia	Beta	0.00047 ± 0.00169	23
Dystonia	Beta	0.00066 ± 0.00155	22, 23
Parkinsonism	Beta	0.00197 ± 0.00203	22, 23
Weight gain	Beta	0.00900 ± 0.00295	22, 23, 25, 44, 45
Diabetes	Beta	0.00008 ± 0.00001	45
Clozapine			
Remission	Beta	0.09109 ± 0.02877	43
Relapse	Beta	0.09136 ± 0.00342	28, 46
Agranulocytosis	Beta	0.00077 ± 0.00278	47
Weight gain	Beta	0.02269 ± 0.01489	47
Diabetes	Beta	0.00124 ± 0.00352	47
Costs			
Medicine costs			
LAI-aripiprazole 400 mg	Gamma	6,848.00 ± 684.80	35
Aripiprazole 10 mg (per tablet)	Gamma	99.74 ± 9.97	35
LAI-paliperidone palmitate 156 mg (equivalent dose of paliperidone 100 mg)	Gamma	6,947.51 ± 694.75	35
LAI-paliperidone palmitate 234 mg (equivalent dose 150 mg)	Gamma	8,914.16 ± 891.41	35
Clozapine 100 mg (per tablet)	Gamma	1.57 ± 0.16	35
Metformin 500 mg (per tablet)	Gamma	0.36 ± 0.04	35
Trihexyphenidyl 2 mg (per tablet)	Gamma	0.20 ± 0.02	35
Propranolol 40 mg (per tablet)	Gamma	0.23 ± 0.02	35
Filgrastim 300 micrograms	Gamma	432.45 ± 43.25	35

TABLE 1. All parameters used in the Markov model. (Continue)

Parameters	Distribution	Mean ± SE	References
Laboratory costs			
HbA1c (per unit)	Gamma	237.21 ± 23.72	48
Serum prolactin (per unit)	Gamma	475.60 ± 47.56	48
Complete blood count (per unit)	Gamma	142.09 ± 14.21	48
Treatments and Additional Procedures			
Hospitalization (per admission)	Gamma	25,610.53 ± 2,561.05	7
OPD service (per visit)	Gamma	592.53 ± 59.25	7
Psychoeducation (per year)	Gamma	3,143.11 ± 314.31	7
Direct non-medical costs			
Travel (per visit)	Gamma	256.11 ± 25.61	7
Meal (per visit)	Gamma	61.66 ± 6.17	48
Utility			
Remission state	Beta	0.690 ± 0.026	40, 41
Relapse state	Beta	0.578 ± 0.028	40, 41
Hyperprolactinemia	Beta	0.618 ± 0.027	38, 41
Akathisia	Beta	0.639 ± 0.056	39-41
Dyskinesia	Beta	0.608 ± 0.040	39-41
Dystonia	Beta	0.449 ± 0.054	40-42
Parkinsonism	Beta	0.626 ± 0.011	39-41
Weight gain	Beta	0.664 ± 0.027	40, 41
Diabetes	Beta	0.664 ± 0.027	40, 41
Agranulocytosis	Beta	0.460 ± 0.059	49

technology assessment in Thailand.[35] Costs of Out-Patient Department (OPD) services, hospitalization, psychoeducation, travel expenses and family time were obtained from previous studies carried out in Thailand.[7] The frequencies of outpatient visits and admissions per year from surveys of mental illness in Thailand were 7.7 and 0.5, respectively.[36]

All costs were adjusted to 2021 values using the consumer price index from the Bureau of Trade and Economic indices, The Ministry of Commerce, Thailand.[37]

Utility values

Quality-adjusted life-years (QALYs) were used for outcomes measurement. The humanistic outcomes were measured in utility weights for different health states and side effects, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life expectancies to generate QALYs.

Utility values of remission states were estimated based on the disability weights according to previous studies.[31] Utility values of other health states were obtained from previous studies.[38-42] All utility values are shown in Table 1.

One-way sensitivity and probabilistic sensitivity analysis

Random Monte Carlo Simulation was applied for probabilistic sensitivity analyses using Microsoft Excel 2020. All variables were randomized and run 1,000 times to generate the probability distribution and the ICER estimation. Beta distribution was used for transition probabilities and utility value, and gamma distribution was used for costs. The results are shown as a cost-effectiveness plane between incremental costs and incremental QALYs. One-way sensitivity analysis was performed using Microsoft Excel 2020. The parameter values were changed individually and regularly to the lowest and highest values. The results of one-way sensitivity analyses were presented in tornado diagram.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis results (presented in Table 2) showed that the total cost of treatment with LAI-aripiprazole and LAI-paliperidone palmitate was LAI-aripiprazole 1,334,919.05 baht and 1,329,818.79 baht, respectively, while the QALYs were 16.35 years for both. Life years of the treatment with LAI-aripiprazole and LAI-paliperidone was 24.27 years and 24.25 years, respectively.

The CER of the treatment with LAI-aripiprazole and LAI-paliperidone palmitate was 81,652.85 baht/QALY gained and 81,330.94 baht/QALY gained, respectively. Due to the significantly lower CER, treatment with LAI-paliperidone palmitate is more cost-effective than treatment with LAI-aripiprazole.

One-way sensitivity and probabilistic sensitivity analysis

Fig 2 presented the one-way sensitivity analysis result in a tornado diagram. According to the findings, the probability of LAI-aripiprazole-induced dyskinesia was the variable with the greatest influence on the ICER. The probabilistic sensitivity analysis result is presented in Fig 3 as a cost-effectiveness plane between the incremental cost and the incremental QALYs of treatment with LAI-aripiprazole compared with LAI-paliperidone palmitate. The Monte Carlo simulations randomized each variable 1,000 times. The red point represents the base-case ICER.

DISCUSSION

A previous economic evaluation study of aripiprazole in Thailand[31] suggested that oral aripiprazole was the dominant strategy, showing greater QALYs and lower

TABLE 2. Cost-effectiveness results.

	Total cost (Baht)	Life Years (Years)	QALYs (Years)	CER (Baht/QALY)
LAI-aripiprazole	1,334,919.05	24.27	16.35	81,652.85
LAI-paliperidone palmitate	1,329,818.79	24.25	16.35	81,330.94

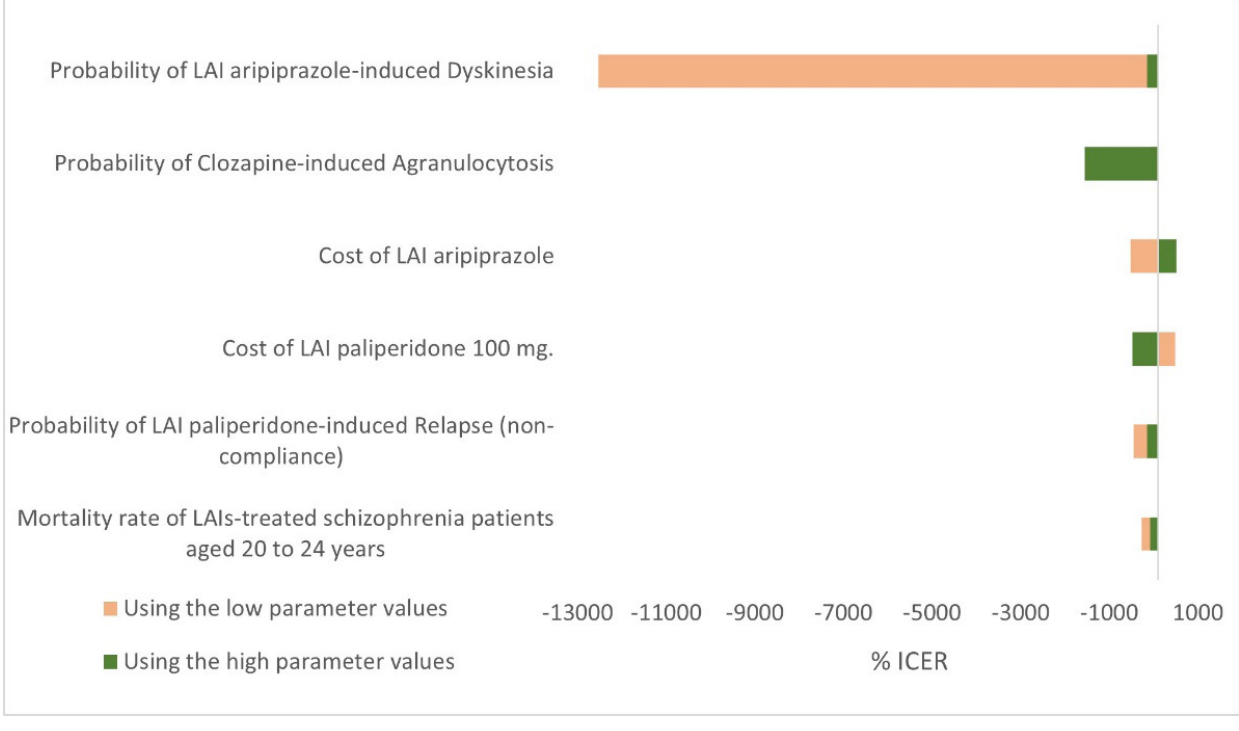

Fig 2. The tornado diagram depicts the results of a one-way sensitivity analysis.

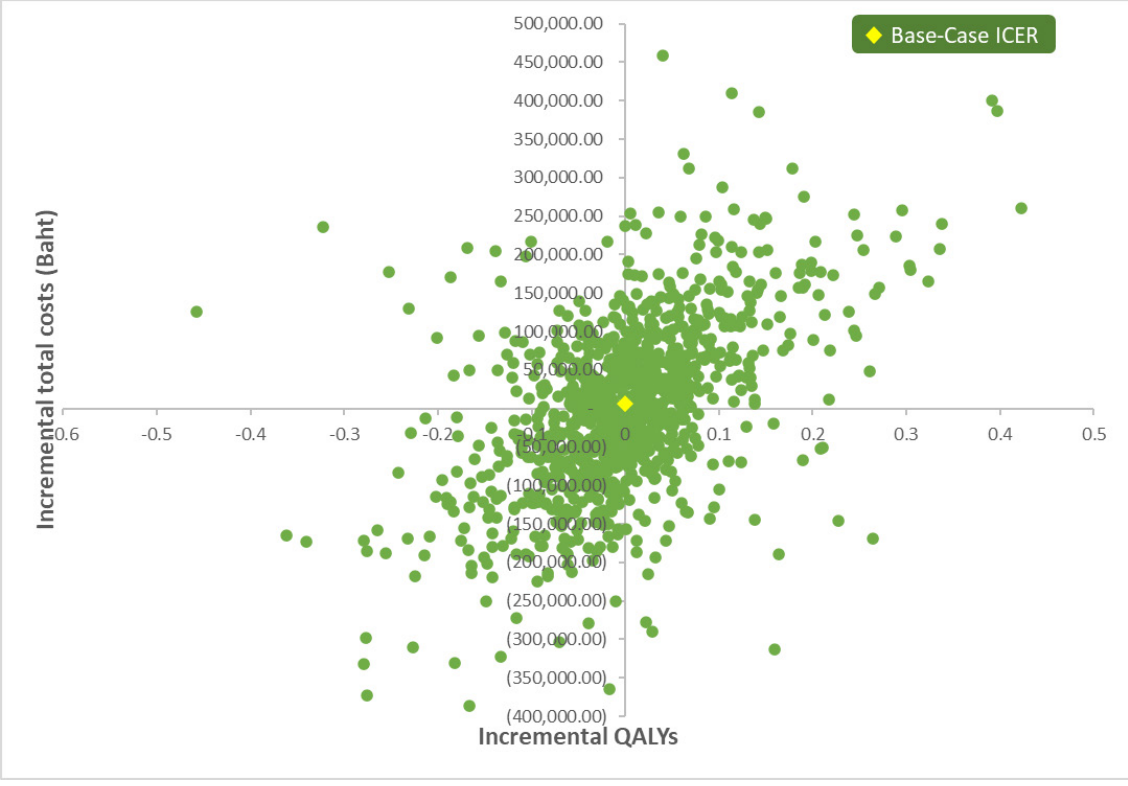

Fig 3. The cost-effectiveness plane of treatment with LAI-aripiprazole compared with LAI paliperidone palmitate.

cost than risperidone in acute schizophrenia patients. However, no previous studies have investigated the economic evaluation of LAI-aripiprazole's use in treating patients with stable schizophrenia. This analysis represented the first economic evaluation comparing LAI-aripiprazole with LAI-paliperidone palmitate for the treatment of stable schizophrenia patients in Thailand. The study revealed that both LAI-aripiprazole and LAI-paliperidone palmitate were similarly beneficial in terms of QALYs, despite the fact that the drug cost of LAI-aripiprazole was cheaper than LAI-paliperidone palmitate. This notion may be considered LAI-aripiprazole as a cost-effective strategy for the treatment of stable schizophrenia patients in Thailand.

Regarding the possible adverse events associated with LAI-aripiprazole or LAI-paliperidone palmitate treatment, such as hyperprolactinemia, akathisia, dyskinesia, dystonia, parkinsonism, diabetes, and weight gain, previous studies conducted in the United States[25,50], the United Kingdom[51], Finland[52] and France[45], only considered and included some of these events in their economic models. In contrast, this study took into consideration all potential adverse events that could impact both costs and utilities, providing a more realistic model that aligns with clinical practices. However, it's worth noting that adverse drug reactions were assumed to be mild, as they were closely monitored every 4 weeks in accordance with the cycle length in the model. Nevertheless, it is important to recognize that despite such monitoring, some adverse events can still occur and may be severe, especially in the short term. The probability of patients experiencing relapse symptoms with once-monthly LAI-aripiprazole treatment was lower than that of those receiving once-monthly LAI-paliperidone palmitate. This could lead to savings in long-term treatment costs. However, from an economic perspective, efficacy is not the only consideration; overall costs, including the treatment of adverse drug events, must also be taken into account. The use of LAI-aripiprazole may result in higher total costs due to the management of side effects, leading to a higher CER. Considering that both LAIs have similar QALYs, LAI-aripiprazole's superior clinical efficacy and longer life expectancy compared to LAI-paliperidone. It's possible that LAI-aripiprazole justifies a 2% price decrease and might be offered LAI-aripiprazole as a dominating strategy for compensating the costs associated with treating side effects, particularly dyskinesia management.

This study encountered some limitations regarding data availability. Specifically, there were few randomized controlled trials (RCTs) that directly compared the efficacy and adverse drug reactions of LAI-aripiprazole with LAI-paliperidone palmitate, and no previous studies were conducted in Thailand. Consequently, the probabilities

of transitioning between health states and experiencing adverse drug reactions were derived from international resources. To enhance the probabilities' validity and minimize the effects of confounding factors, sensitivity analysis was performed based on global data. Additionally, utility values were obtained and recalculated into utility weights specifically for Thai schizophrenia patients. The use of different values from various data sources and diverse populations resulted in a notable variation in the likelihood of side effects and efficacy for each patient receiving LAI treatment. This variability holds the potential to significantly impact the overall treatment outcome, as manifested by the conspicuous amplitude of sensitivity dispersion observed among the sensitivity results. Moreover, this study did not include sexual dysfunction and neuroleptic malignant syndrome (NMS) as adverse drug reactions of antipsychotics due to their rarity and the limited availability of relevant data.

Further economic evaluation studies are required to evaluated the cost-effectiveness of LAI-aripiprazole and LAI-paliperidone palmitate using the real-word data in Thai stable schizophrenia patients to provide a more accurate and reliable evaluation.

CONCLUSION

In Thailand, the treatment of stable schizophrenia with LAI-aripiprazole was found to yield similarly beneficial results in terms of QALYs when compared to treatment with LAI-paliperidone palmitate, despite being more costly. Comparatively, LAI-aripiprazole exhibited better clinical efficacy and led to a longer average life expectancy than LAI-paliperidone. If the drug cost of LAI-aripiprazole were decreased by 2%, treatment with LAI-aripiprazole would become a dominant cost-effectiveness strategy. The results of this study could contribute to informed decision-making by policymakers.

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Burnout and Associated Factors among Thai Anesthesiology Residents

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ABSTRACT

Objective: The study evaluates the prevalence of burnout and the associated risk factors among Thai anesthesiology residents.

Materials and Methods: This cross-sectional study was conducted by an online questionnaire and sent 385 anesthesiology residents in Thailand. The questionnaire consisted of a consent form, personal information, potential risk factors of burnout, and the Thai version of the Copenhagen Burnout Inventory-Student Survey (CBI-SS).

Results: A total of 248 respondents completed the questionnaire. The overall prevalence of burnout among Thai anesthesiology residents was 35.5%. Sleeping for 5-6 hours (odds ratio 3.68, 95% CI 1.40 to 9.68, p = 0.008), sleeping less than 5 hours (odds ratio 6.89, 95% CI 1.90 to 24.92, p = 0.003), along with dissatisfaction and the idea of discontinuation of training, were associated with higher burnout (odds ratio 8.38, 95% CI 3.65 to 19.25, p < 0.001 and odds ratio 3.11, 95% CI 1.57 to 6.18, p = 0.001, respectively). Compared to first-year residents, second-year residents exhibited a lower risk of burnout (odds ratio 0.32, 95% CI 0.134 to 0.76, p = 0.009) while no significant difference among third-year residents (odds ratio 0.54, p = 0.17, 95% CI 0.25-1.17).

Conclusion: The prevalence of burnout among Thai anesthesiology residents was high. Sleeping less than 7 hours, experiencing dissatisfaction, and contemplating discontinuation of training were associated with a higher risk of burnout, while being a second-year resident lowered the risk.

Keywords: Burnout; anesthesiology; resident; Thailand (Siriraj Med J 2023; 75: 736-743)

INTRODUCTION

Burnout is a work-related syndrome characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment.[1] It responds to chronic job-related stressors and is exclusively associated with the work environment. Burnout has been associated with strained relationships among team members[2], leading to adverse effects on health and overall quality of life. Physicians have reported increasing levels of stress and burnout[3], which can have detrimental effects on the quality of patient care and potentially contribute to medical errors.[4,5]

Anesthesiologists exhibit a relatively high prevalence of burnout. The prevalence of burnout among anesthesiology varies across studies, ranging from 13.8% for burnout syndrome to as high as a 59% risk of burnout.[6,7] Of particular concern is the high risk of burnout during residency training. A survey conducted among anesthesiology residents in the United States found that 41% were at high risk of burnout.[8] The precise reasons of anesthesia residents' burnout remain unclear. However, it is plausible that they lack experience and need to acquire knowledge, cognitive abilities, and technical skills, as well as adapt to efficient perioperative teamwork, which contributes to this heightened risk.

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Objective: No study has reported on the prevalence of burnout among Thai anesthesia residents. The study objective is to evaluate the prevalence, and possible factors associated with burnout among Thai anesthesia residents.

MATERIALS AND METHODS

Cross-sectional study

Following the approval from the Ethics Committee of Thammasat University (COA No.023/2566), the data collection period took place from January 22, 2023, to February 12, 2023.

Participants

Inclusion criteria were Thai anesthesiology residents who were in the Thai anesthesia training program during the study period. Anesthesia residents who declined to answer the questionnaire were excluded.

Questionnaire

The Questionnaires consisted of four sections: a consent form, personal data, potential risk factors of burnout, and the Thai version of the Copenhagen Burnout Inventory Student Survey (Thai CBI-SS). The questionnaire was developed using the online Google Forms application. A research assistant reached out to the representatives of 14 institutions throughout Thailand that host anesthesia resident training programs to share the online questionnaire with all anesthesia residents. Participants could accept or decline answering it. All responses were collected anonymously. To ensure maximum participation, the research assistant sent reminders once a week for three consecutive weeks.

Participants were asked to furnish details about their demographic characteristics (including gender, age, marital status, years of resident training, underlying disease, income, smoking habits, alcohol consumption, and exercise habits). The potential risk factors of burnout were reviewed in relevant literature.[7,8-10] These factors included working hours, shift hours, adequacy of consultation, sleep duration, workplace resources, job support at work and at home, satisfaction with resident training, an idea to discontinue training, as well as demographic characteristics data. The final section was the Thai version of the Copenhagen Burnout Inventory Student Survey (Thai CBI-SS). The Thai CBI-SS consisted of a comprehensive set of twenty-five questions categorized into four domains: personal burnout (six items), study-related burnout (seven items), colleague-related burnout (six items), and teacher-related burnout (six items). Each item was rated on a five-point Likert scale, ranging from '100 (always)' to '0 (never/almost never)'. Scores between 50 and 74 were categorized as 'moderate' burnout, scores between 75 and 99 were classified as 'high' burnout and a score of 100 indicated severe burnout.

The Copenhagen Burnout Inventory (CBI), developed by Kristensen TS[11], has demonstrated good reliability and validity as a measure of burnout. Winwood and Winefield[12] confirmed that the CBI effectively conceptualizes burnout, and exhibits strong reliability and validity. Moreover, the Copenhagen Burnout Inventory-Student Survey (CBI-SS)[13] has been acknowledged as a reliable and valid instrument for evaluating burnout among medical students. Correlational analyses between CBI-SS and the Maslach Burnout Inventory-Student Survey (MBI-SS), a widely-used standardized tool, have revealed moderate to strong correlations. The CBI-SS has undergone linguistic translation and cultural adaptation into several languages, including Thai. Research has validated the Thai version of the Copenhagen Burnout Inventory-Student Survey (CBI-SS) and demonstrated its reliability as an effective tool for evaluating burnout syndrome among preclinical medical students in Thailand.[14]

Although anesthesia residents are part of a postgraduate training program, in the Thai cultural educational system, Thai residents interact with the staff in a teacher/student relationship. The decision was made to utilize the CBI-SS instead of the CBI because the CBI-ss has a teacher-related burnout question domain.

Statistical analysis

The sample size was calculated based on a previous report of the prevalence of burnout (41%), with an acceptable margin of error (0.05). The calculated sample size was 372. The decision was made to recruit all Thai anesthesia residents at the time of the study, which totaled 385 considering the survey dropout rate. The data were analyzed using StataCorp. Version 17. College Station, TX: StataCorp LLC; 2021. Descriptive statistics summarized the characteristics. Categorical variables were depicted in the form of frequencies and percentages. Continuous variables were described using either means with standard deviations or medians with interquartile ranges. For comparing continuous variables, t-tests or Wilcoxon rank-sum tests were employed. Categorical variables were compared using either chi-square tests or Fisher exact tests. Logistic regression analysis identified predictors of burnout. Univariate associations were initially examined, and factors with a p-value < 0.1 were included in the multivariable logistic regression model to identify independent risk factors. Results were reported as odds ratios with 95% confidence intervals. A p-value < 0.05 indicated statistical significance.

RESULTS

Out of the 385 Thai anesthesia residents from 14 institutions who were invited to participate in the online questionnaire, a total of 250 individuals responded, resulting in a response rate of 64.94%. Among the respondents, 248 participants completed all the questions, while 2 residents declined to answer the questionnaire.

Physician characteristic

The majority of respondents, 200 were female (80.65%). The median age was 29 years old, with a range of 27 to 30 years. Among the respondents, there were 77 first-year residents (31.05%), 77 second-year residents (31.05%), and 94 third-year residents (37.90%) who completed the questionnaire.

Regarding underlying disease, 15 individuals (6.05%), reported underlying diseases including allergic rhinitis, polycystic ovary syndrome, gastritis, obstructive sleep apnea, migraine, and Glucose-6-Phosphate Dehydrogenase deficiency. Five residents (2.02%) had a major depressive disorder. Further details of participant characteristics are shown in Table 1.

Prevalence

The prevalence of burnout among Thai anesthesia residents who responded to the questionnaire was 35.48% (95% CI 0.30 to 0.42), with 33.06% experiencing moderate burnout and 2.42% experiencing high burnout. No participants reported severe burnout. These findings indicate that burnout is a significant concern among Thai anesthesia residents.

Factors associated with burnout

The univariate analysis was conducted to screen factors associated with burnout and found ten factors associated with burnout. The results are presented in Table 2. Following the screening procedure, a multivariable logistic regression analysis was conducted to validate the findings, identifying four significant factors which are sleep duration, year of resident training, dissatisfaction, and having an idea of discontinuation of resident training associated with burnout. The result is shown in Table 3.

Sleeping less than 7-8 hours was identified as a significant risk factor for burnout, particularly among residents who slept less than 5 hours (odds ratio 6.89, 95% CI 1.90 to 24.92, P = 0.003). Additionally, residents who slept for 5-6 hours also had a higher risk of burnout (odds ratio 3.68, 95% CI 1.40 to 9.68, P = 0.008).

Dissatisfaction with resident training and having an idea of stopping resident training were found to be significant risk factors for burnout (odds ratio 8.38, 95% CI 3.65 to 19.25, P = 0.00, and odds ratio 3.11, 95% CI 1.57 to 6.18, P = 0.001, respectively).

Compared to first-year residents, second-year residents had a significantly lower risk of burnout (odds ratio 0.32, 95% CI 0.134 to 0.76, P = 0.009). However, no significant difference was observed between third-year residents and first-year residents (odds ratio 0.54, P = 0.17, 95% CI 0.25 to 1.17).

DISCUSSION

The prevalence of burnout among Thai anesthesiology residents is high at 35.48%, although lower than reported in the United States by Oliveira et al. (41%)[8] and Huaping Sun (51%).[9] Various factors may contribute to this difference, including individual variations, cultural influences, and differences in training programs between countries. Additionally, the study's sample size may have influenced the prevalence rate, as only 66.67% (248 of 372) of the target sample size was recruited. However, this online response rate of 64.94% is higher than the average reported in recent meta-analyses of online surveys which was around 44.1%.[15]

The multivariable logistic regression analyses identified factors including sleeping time, year of training, satisfaction with the training program, and the idea of discontinuation of training that were significantly associated with burnout among Thai anesthesiology residents. The results align with previous research[10,16] that has found an association between insufficient sleep and increased risk of burnout. In this study, sleeping less than 7 hours increased the burnout risk. Insufficient sleep can have various physical, cognitive, and emotional effects that increase stress levels and make individuals more susceptible to burnout. While this study focused on sleep duration, Hannah K. Allen[17] has found an association between the poor quality of sleep which is characterized by difficulties falling asleep or frequent awakenings, and burnout. Additionally, Chatlaong T found an association between sleep quality and emotional exhaustion, which is a component of burnout among resident trainees.[18] However, our questionnaire evaluated only the duration, not the quality, of sleep. It would be valuable for future studies to consider evaluating both sleep duration and quality to provide more understanding of the relationship between sleep and burnout.

According to the research conducted by Huaping Sun and De Oliveira GS[8,9], it was discovered that an increase in the age of physician trainees corresponded to a reduced risk of experiencing burnout. The second-year residents had a significantly lower risk of burnout compared to first-year residents, while there was no

TABLE 1. Descriptive statistics of respondent characteristics.

Characteristic	N 248
Sex	
Male	48 (19.35)
Female	200 (80.65)
Year of resident training	
3rd year	94 (37.90)
2nd year	77 (31.05)
1st year	77 (31.05)
Age	29 (27-30)
Marital status	
Single	139 (56.05)
Married	17 (6.85)
In relationship	92 (37.10)
Have children	5 (2.02)
Have underlying disease	15 (6.05)
Have Psychological disease	5 (2.02)
Smoking	2 (0.81)
Alcohol drinking	128 (51.61)
Exercise	
Routine	16 (6.45)
Sometimes	125 (50.4)
No	107 (43.15)
Official working hours per month	
>160	119 (47.98)
128-160	115 (46.37)
80-120	14 (5.65)
Shifts hours per month	
>160	13 (5.24)
128-160	54 (21.77)
88-120	73 (29.44)
40-80	97 (39.11)
<40	11 (4.44)
Income	
Enough to save	8 (3.23)
Enough to spend	75 (30.24)
Not enough	165 (66.53)
Sleeping time (hours)	
7-8	31 (12.50)
5-6	169 (68.15)
<5	48 (19.35)
Dissatisfaction with resident training	62 (25)
Having thought about discontinuing training*	114 (45.97)
Job support at home	
No support	198 (79.84)
Not enough	43 (17.34)
Enough	7 (2.82)
Job support at work	
No support	75 (30.24)
Not enough	153 (61.69)
Enough	20 (8.07)
Resource for working	
Not enough	118 (47.58)
Enough but not easy to use	92 (37.10)
Enough and easy to use	38 (15.32)
Consultation	
No consultation	122 (49.19)
Not enough	95 (38.31)
Enough	31 (12.5)

Data are presented as number (%) or median (range). *One piece of data is missing from the answers of 248 participants.

significant difference among third-year residents. A possible explanation for this finding is that second-year residents have had more time to adapt to their work, studies, and interactions with colleagues and the work environment. They may have gained more experience and developed better coping strategies, which could contribute to a lower risk of burnout. On the other hand, first-year residents are faced with the challenges of acquiring new knowledge and navigating stressful situations which could increase their risk of burnout. Interestingly, our study did not find a significant difference in burnout risk between first-year and third-year residents. This could be attributed to the fact that third-year residents carry higher responsibilities, face greater expectations, and need to maintain high levels of concentration as they prepare for the board-certified examination. These factors may offset the additional experience they have gained.

Residents who expressed dissatisfaction with the training program and considered discontinuing their training had a significantly higher risk of burnout. The association between burnout and job satisfaction has been observed in previous studies, such as Govardhan LM's study, which found an inverse correlation between burnout

TABLE 2. Univariate analysis for factors associated with burnout.

Variable	Risk of burnout	Univariate		
		P value	OR	95%CI
Gender				
Female	68 (34.00)	0.32	0.72	0.38-1.37
Male	20 (41.67)			
Age		0.626	1.04	0.90-1.20
Year of resident training				
3rd year	31 (32.98)	0.020	0.48	0.26-0.89
2nd year	18 (23.38)	0.001	0.30	0.15-0.59
1st year	39 (50.65)			
Marital status				
Married	6 (35.29)	0.573	0.74	0.26-2.11
In relationship	23 (25.00)	0.007	0.45	0.25-0.81
Single	59 (42.44)			
Have children				
Yes	2 (40.00)	0.831	1.22	0.20-7.42
No	86 (35.39)			
Underlying disease				
Yes	8 (53.33)	0.144	2.19	0.77-6.24
No	80 (34.33)			
Psychological disease				
Yes	2 (40.00)	0.831	1.22	0.20-7.42
No	86 (35.39)			
Smoking				
No	88 (35.77)	0.540		
Yes	0 (0.00)			
Alcohol drinking				
Yes	44 (34.38)	0.706	0.9	0.54-1.52
No	44 (36.67)			
Exercise				
Sometimes	49 (39.20)	0.140	1.51	0.87-2.61
Regular	7 (43.75)	0.272	1.82	0.62-5.32
No	32 (29.90)			
Income				
Not enough	5 (62.50)	0.056	4.18	0.96-18.21
Enough for spending	36 (48.00)	0.004	2.32	1.32-4.08
Enough for saving	47 (28.48)			
Official working hours per month (hour)				
>160	58 (48.74)	0.017	12.36	1.57-97.51
128-160	29 (25.22)	0.163	4.38	0.55-34.99
80-120	1 (7.14)			

TABLE 2. Univariate analysis for factors associated with burnout. (Continue)

Variable	Risk of burnout	Univariate		
		P value	OR	95%CI
Shift hours per month				
>160	4 (30.77)	0.851	1.19	0.20-6.99
128-160	14 (25.93)	0.926	0.93	0.22-4.02
88-120	19 (26.03)	0.930	0.94	0.23-3.91
40-80	48 (49.48)	0.174	2.61	
<40	3 (27.27)			
Sleeping time (hour)				
<5	20 (64.52)	<0.001	6.91	2.51-19.03
5-6	58 (34.32)	0.079	1.99	0.92-4.27
7-8	10 (20.83)			
Resource for working				
Not enough	21 (55.26)	0.003	3.18	1.50-6.77
Enough but not easy to use	34 (36.96)	0.167	1.51	0.84-2.71
Enough and easy to use	33 (27.97)			
Consultation				
No consultation	20 (64.52)	<0.001	4.71	2.04-10.85
Not enough	34 (35.79)	0.213	1.44	0.81-2.57
Enough	34 (27.87)			
Satisfaction with resident training				
Dissatisfy	46 (74.19)	<0.001	9.86	5.07-19.16
Satisfy	42 (22.58)			
Having thought about discontinuing training				
Yes	66 (57.89)	<0.001	6.94	3.85-12.51
No	22 (16.54)			
Job support at home				
No support	3 (42.86)	0.769	1.26	0.27-5.77
Not enough	11 (25.58)	0.146	0.58	0.27-1.21
Enough	74 (37.37)			
Job support at work				
No support	14 (70.00)	<0.001	12.25	3.92-38.24
Not enough	62 (40.52)	<0.001	3.58	1.78-7.18
Enough	12 (16.00)			

CI = confidence interval, OR = odds ratio, significant at P ≤0.0, risk of burnout are presented as number (%)

and job satisfaction among obstetrics and gynecology residents.[19] Factors contributing to job satisfaction are influenced by various details. Unfortunately, our questionnaire did not explore the specific reasons behind residents' dissatisfaction or desire to discontinue training. Further research is needed to investigate these causes for improvement in training programs.

Regarding other factors related to burnout, some previous studies have reported factors to be associated with an increased risk of burnout, such as younger age[20-22], female gender[8,20], marital status[21], having children[22], high alcohol consumption[8], lack of job support[7,21], and high workload.[7-9,22] Conversely, having sufficient work resources has been found to decrease the risk of burnout[9].

TABLE 3. Multivariable logistic regression analysis for factors associated with burnout.

Associated factors	Multivariable analysis		
	OD	95%CI	P value
Year of resident training			
1st year			
2nd year	0.32	0.134-0.76	0.009
3rd year	0.54	0.25-1.17	0.17
Sleeping time (hour)			
<5	6.88	1.90-24.93	0.003
5-6	3.68	1.40-9.68	0.008
7-8			
Satisfaction with resident training			
Dissatisfy	8.38	3.65-19.25	0.00
Satisfy			
Thought of discontinuing training			
Yes	3.112	1.57-6.18	0.001
No			

CI = confidence interval, OR = odds ratio, significant at P ≤0.05

However, our investigation yielded no significant association between these factors and burnout, which is consistent with findings from several other studies that reported no association between burnout and female gender[21,22] or marital status.[8] Regarding workload, we did not find a significantly increased risk of burnout, despite the association reported in many studies. One possible explanation could be the way the question was asked, which separated official work hours and shift hours per month, rather than capturing all the working hours per week. This might have made it challenging to accurately estimate the exact workload per week and could have influenced the results.

The present study has several limitations. Firstly, the study relied on self-reported data, which introduces the possibility of social desirability bias. Secondly, the sample size was lower than the calculated sample size. This could have affected the generalizability of the findings. The smaller sample size could also have limited the statistical power to detect significant associations. Thirdly, the unclear wording of questions regarding working hours may adversely impact the result. Lastly, the study did not explore certain potential risk factors in depth, such as the quality of sleep or the specific reasons for dissatisfaction with the training program. Future research could be conducted to explore the factors contributing to burnout. This research would help in developing suitable support measures to support residents.

In conclusion, the prevalence of burnout among Thai anesthesiology residents was high. Sleeping less than 7 hours, experiencing dissatisfaction, and contemplating discontinuation of training were identified associated with a higher risk of burnout, while being a second-year resident lowered the risk.

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Conflict of interest statement

The authors declare no conflict of interest

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Associated Factors of Quality of Life in Adult Female Acne Coexisting with Hyperandrogenism and Polycystic Ovarian Syndrome using the Dermatology Life Quality Index

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ABSTRACT

Objective: This study aimed to assess the effects of AFA and its associated factors, especially those coexisting with hyperandrogenism or PCOS, on QoL using the Dermatology Life Quality Index (DLQI).

Materials and Methods: A retrospective cross-sectional study was conducted on AFA patients who had been treated between May 2018 and January 2020. Dermatologists had performed history taking and determined the clinical severity of the acne, and gynecologists had identified PCOS. Aggravating factors and DLQI were self-reported by the patients.

Results: A total of 208 AFA patients, aged 31.8±7.1 years on average, were included. The mean DLQI score was 8.0±5.4 (range: 0-23). Patients with moderate to severe acne had significantly higher total DLQI scores compared to those with almost clear to mild acne (P=0.043). Similarly, patients who reported acne aggravated by diet, androgenetic alopecia, or perioral and chin lesions had significantly higher total DLQI scores (P=0.025, P=0.049, and P=0.014, respectively). However, PCOS and hirsutism did not significantly impact QoL. The aspect most affected was feeling embarrassed and self-conscious, with significantly greater impacts observed in patients with moderate to severe acne compared to mild acne. The daily activities of patients with androgenetic alopecia were significantly impacted in terms of their choice of clothes and sexual difficulties.

Conclusion: AFA mostly had a moderate to extremely large effect on patients' QoL. Knowing the factors influencing QoL, such as acne severity, dietary aggravation of acne, and androgenetic alopecia, may enable physicians to improve the QoL of patients.

Keywords: Acne; adult female acne; DLQI; quality of life; hyperandrogenism; androgenetic alopecia (Siriraj Med J 2023; 75: 744-751)

INTRODUCTION

Acne vulgaris is one of the most prevalent dermatological diseases. It is commonly found in adolescents but can sometimes persist through adulthood.[1] It is generally accepted that acne negatively impacts patients' lives, including embarrassment and limitations to daily and social activities.[2] The impact of acne is evident in the form of decreases in the quality of life (QoL) that are as severe as those found with other debilitating diseases, such as asthma, epilepsy, diabetes mellitus, back pain, and arthritis.[3] "Adult female acne" (AFA) is defined as acne in women over the age of 25.[4-6] Previous reports

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have mentioned that AFA affects mental and emotional health, social and personal behavior, and QoL.[7,8]

Acne vulgaris is also one of the signs of hyperandrogenism and polycystic ovary syndrome (PCOS), which also negatively affect patients' QoL.[9] QoL is a crucial aspect of the morbidity related to acne, and it is an essential consideration when determining treatments. The number of studies specifically exploring QoL in AFA is limited, especially in AFA with PCOS, and few factors associated with QoL have been identified.[10,11] Several dermatological questionnaires are available to measure the impact of skin disorders on QoL. One of these is the Dermatology Life Quality Index (DLQI), a 10-item self-administered questionnaire to measure the effects of skin diseases on patients' QoL. It has been translated and validated in many languages, including Thai.[12,13]

This study aimed to assess the effects on patients' QoL of AFA (especially AFA coexisting with hyperandrogenism or PCOS) and associated factors. Assessments were made using the Thai version of the DLQI.

MATERIALS AND METHODS

This retrospective cross-sectional study was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 1043/2021). We enrolled female patients aged 25 or older who presented with AFA disease at the Siriraj Dermatology Clinic between May 2018 and January 2020 and had DLQI scores in their medical records. Patients were excluded if they had been previously treated with any systemic therapy for acne or if no DLQI information was available.

Demographic characteristics and acne-related information were gathered. The data comprised patient age, onset subtype, precipitating cause of acne flare, type and sites of lesions, extent of acne lesions, blood pressure, body weight, height, and waist circumference. Acne presenting in women aged 25 or older was defined as AFA,[4,5] whereas acne in women older than 45 was referred to as "perimenopausal acne."[14] The onset of AFA is classified into 3 subtypes: persistent, late-onset, and relapsed.[5] Acne developing in adolescence and continuing into adulthood is deemed "persistent acne," whereas acne that first occurs after age 25 is called "late-onset acne." Acne that occurs during adolescence for a few years and then reoccurs after 25 is termed "relapsed acne."

All patients were evaluated for acne severity by dermatologists using the Investigator's Global Assessment. The severities were classified as follows:[15]

- "Almost clear:" rare comedones or 1 inflammatory lesion
- "Mild:" some comedones with few inflammatory lesions without nodular lesions
- "Moderate:" up to many comedones with some inflammatory papules but no more than 1 small nodular lesion
- "Severe:" many comedones and inflammatory papules, and few nodular lesions
- "Very severe:" many comedones, inflammatory papules, and nodular lesions

The skin signs of hyperandrogenism, including androgenetic alopecia and hirsutism, were recorded. "Androgenetic alopecia" (AGA) was defined as grade I or more under Ludwig's classification.[16] In Asian populations, a Modified Ferriman–Gallwey score of ≥ 6 indicates hirsutism,[16] and a body mass index (BMI) ≥ 23 kg/m^2 denotes an overweight or obese status.[17]

Gynecologists evaluated PCOS with the consent of the AFA patients. Diagnoses of this condition were based on recommendations from international evidence-based guidelines for assessing and managing PCOS.[16] QoL impairment was recorded using the validated Thai version of the DLQI.[13] The questionnaire has 10 items that evaluate 6 dermatological aspects of life: symptoms and feelings, daily activities, leisure activities, work or school, personal relationships, and treatment. Each item has a score ranging from 1 to 3. The total DLQI score is calculated by summing the scores for the 10 items, giving a possible maximum of 30 and a minimum of 0. Higher scores signify greater degrees of impairment of QoL. The total DLQI scores are interpreted as follows: 0–1, no effect on QoL; 2–5, small effect; 6–10, moderate effect; 11–20, very large effect; and 21–30, extremely large effect.[12,13]

The statistical analysis was undertaken using IBM SPSS Statistics for Macintosh, version 27.0 (IBM Corp., Armonk, NY, USA). Data are presented as numbers and percentages, means and standard deviations, and ranges. Mean differences between continuous variables were calculated by an independent *t*-test or 1-way ANOVA. Differences in categorical data were calculated by the chi-squared test or Fisher's exact test. Statistical significance was set at $P < 0.05$, and the results are reported with a 95% confidence interval.

RESULTS

Two hundred and eight AFA patients were included. Their mean age was 31.8 ± 7.1 years, ranging from 25.2 to 59.4 years. Perimenopausal acne was identified in 14 patients (6.7%). Most patients presented with persistent acne (47.1%); late-onset and relapsed acne accounted for 26.9% and 26.0% of cases, respectively. Half of the

patients (51%) had moderate severity of acne, followed by mild acne (38%), severe acne (8.1%), and almost clear acne (2.9%). Twenty-four patients (11.5%) had hirsutism, and 12 (5.8%) had AGA. Fifty-four patients consented to undergo evaluations by gynecologists, of whom 26 (48.1%) were diagnosed with PCOS.

All patients completed all 10 questions of the DLQI questionnaire. The overall mean DLQI score was 8.0 (standard deviation, 5.4; range, 0–23). No, small, moderate, very large, and extremely large effects on QoL were found in 8.2%, 32.7%, 29.3%, 27.4%, and 2.4% of patients, respectively. The mean total DLQI scores for each characteristic are detailed in Tables 1 & 2. Perimenopausal acne had lower mean total DLQI scores than non-perimenopausal acne, with no significant differences noted. All acne subtypes had a moderate effect on QoL, whereas late-onset acne had the lowest mean total DLQI scores. Patients with moderate to severe acne had significantly higher mean total DLQI scores than patients with almost clear to mild acne ($P = 0.043$).

Regarding promoting factors, patients who reported that diet was related to acne had a significantly higher mean total DLQI score than those who did not ($P = 0.025$). Stress, sleep deprivation, pre-menstruation, sunlight, dust, and exercise did not significantly affect the mean total DLQI scores. Patients with cosmetic products promoting acne had significantly lower mean total DLQI scores ($P = 0.018$).

As for the risk for metabolic syndrome, patients with moderate to severe acne had a significantly higher mean BMI (22.6 ± 4.4) than patients with almost clear to mild acne (21.4 ± 3.1) ($P = 0.031$). However, the mean DLQI score of patients at risk of metabolic syndrome did not differ from that of patients with AFA who did not have the risk. In addition, AFA with AGA had a significantly greater mean total DLQI score (11.0 ± 7.4) than AFA without AGA ($P = 0.049$). However, significant differences were not found between AFA with and without hirsutism, or between AFA with and without PCOS.

A comparison of the DLQI scores for the various acne characteristics is presented in Table 2. Regarding the sites of acne lesions, patients with acne in the perioral area and chin had significantly greater mean total DLQI scores than those without such lesions ($P = 0.014$). More extensive acne resulted in higher total DLQI scores, especially when comparing the mean total DLQI score for 1 site versus the involvement of ≥ 2 sites ($P = 0.05$). Mixed comedones and inflammatory papules had the highest mean total DLQI scores.

Concerning DLQI, the dermatological aspect of life most frequently affecting patients was feeling embarrassed and self-conscious. This factor had the highest mean ± SD score (1.7 ± 1.0) and was followed by symptoms, leisure activities, and daily activities (Table 3). Regarding the severity of acne, patients with moderate to severe acne reported greater impacts on feeling embarrassed and self-conscious, daily activities, and leisure activities than those with mild acne. As mentioned earlier, patients with AGA experienced a marked impact on their QoL compared with patients without AGA. In particular, the daily activities of patients with AGA were significantly impacted in terms of their choice of clothes and sexual difficulties. As for age, most aspects of DLQI did not vary by age; the exception was perimenopausal acne, which had relatively less effect on the choice of clothes.

DISCUSSION

This study highlights that AFA can have moderate to substantial effects on QoL. Patients with AFA in the perimenopausal group tended to have a better QoL than those in the non-perimenopausal group. This difference may result from younger patients paying more attention to their appearance, thereby negatively affecting their social and personal lives. However, *Lasek* et al. reported that acne had greater effects on the QoL of older patients,[18] which may be due to differences in self-perception related to ethnicity. A previous study showed that even mild acne could enormously affect patients' QoL.[19, 20] In the current investigation, 17.6% of the patients with almost clear to mild acne reported very large effects on their QoL. Although previous studies reported no correlation between acne clinical severity and QoL scores,[3,21] our work revealed a correlation between the impact of acne on QoL and the severity of acne. The clinical severity of acne among AFA patients affected their QoL more than the subtype of acne.

According to the effects of aggravating factors and the QoL, the patients with diet-aggravated acne stated that they had a worse QoL than those who did not report that diet exacerbated the condition. In addition, in our study on adult acne patients, those who reported the use of cosmetic products that exacerbated their acne also exhibited a significantly lower impact on their quality of life, possibly suggesting a potential link between the use of cosmetics and the role of cosmetic camouflage, although further investigation is required to elucidate this relationship.

Feeling embarrassed was the aspect that mainly affected QoL in cases of AFA, which is consistent with earlier studies on acne patients in Thailand.[19,20] An extensive study on different racial groups also reported that AFA

TABLE 1. Demographic, clinical characteristics, and the Dermatology Life Quality Index of adult female patients with acne (N = 208).

Demographic data		Number (%)	Mean total DLQI scores (SD)	Range	*P* value
Age groups of patients (years)					0.18
25 - 44		194 (93.3)	8.15 (5.5)	0-23	
45 - 60		14 (6.7)	6.14 (4.0)	1-14	
Onset subtypes of acne					0.92
Persistent acne		98 (47.1)	8.03 (5.5)	0-23	
Late-onset acne		56 (26.9)	7.80 (5.6)	0-22	
Relapse acne		54 (26.0)	8.22 (5.1)	0-22	
Investigator's Global Assessment Scale for acne severity					**0.043***
Almost clear to mild		85 (40.9)	7.11 (5.4)	0-21	
Moderate to severe		123 (59.1)	8.65 (5.4)	1-23	
Promoting factors					
Pre-menstruation	Yes	151 (72.6)	8.25 (5.6)	0-23	0.32
	No	57 (27.4)	7.40 (4.8)	0-20	
Stress	Yes	112 (53.8)	8.29 (5.4)	0-21	0.45
	No	96 (46.2)	7.71 (5.5)	0-23	
Sleep deprivation	Yes	108 (51.9)	7.69 (5.3)	0-21	0.37
	No	100 (48.1)	8.37 (5.6)	0-23	
Diet	Yes	71 (34.1)	9.18 (5.3)	1-21	**0.025***
	No	137 (65.9)	7.42 (5.4)	0-23	
Sunlight	Yes	35 (16.8)	9.00 (5.6)	1-21	0.24
	No	173 (83.2)	7.82 (5.4)	0-23	
Cosmetic products	Yes	29 (13.9)	6.24 (4.0)	1-17	**0.018***
	No	179 (86.1)	8.31 (5.6)	0-23	
Dust	Yes	14 (6.7)	8.14 (6.4)	1-22	0.93
	No	194 (93.3)	8.01 (5.4)	0-23	
Exercise	Yes	11 (5.3)	8.91 (5.4)	1-20	0.58
	No	197 (94.7)	7.97 (5.4)	0-23	
Patients at risk for metabolic syndrome					
Waist circumference >80 cm	Yes	58 (27.9)	8.76 (5.4)	1-22	0.22
	No	150 (72.1)	7.73 (5.4)	0-23	
SBP >130 or DBP >85 mmHg	Yes	24 (11.5)	9.21 (5.6)	1-20	0.25
	No	184 (88.5)	7.86 (5.4)	0-23	
BMI ≥23 kg/m^2 (overweight-obese status)	Yes	68 (32.7)	8.68 (5.4)	1-22	0.22
	No	140 (67.3)	7.70 (5.4)	0-23	
Hirsutism (Modified Ferriman–Gallwey Score of ≥6)					0.33
Yes	24 (11.5)	9.04 (5.7)	1-21		
No	184 (88.5)	7.89 (5.4)	0-23		
Androgenetic alopecia					**0.049***
Yes		12 (5.8)	11.0 (7.4)	0-23	
No		196 (94.2)	7.84 (5.2)	0-22	
PCOS diagnosis					0.06
Yes		26/54 (48.1)	6.38 (5.0)	0-18	
No		28/54 (51.9)	9.43 (6.4)	1-23	

*A *P* value <0.05 indicates statistical significance.

Abbreviations BMI, body mass index; DBP, diastolic blood pressure; DLQI, Dermatology Life Quality Index; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; SD, standard deviation

TABLE 2. The Dermatology Life Quality Index scores for different characteristics of acne.

Clinical characteristics		Number (%)	Mean total DLQI scores (SD)	Range	*P* value
Sites of acne lesions					
Forehead and temples	Yes	145 (69.7)	7.91 (5.0)	1-23	0.69
	No	63 (30.3)	8.27 (6.4)	0-22	
Nose	Yes	25 (12.0)	8.52 (5.8)	1-22	0.62
	No	183 (88.0)	7.95 (5.4)	0-23	
Cheeks	Yes	181 (87.0)	7.93 (5.3)	0-23	0.59
	No	27 (13.0)	8.63 (6.4)	0-20	
Perioral area and chin	Yes	170 (81.7)	8.45 (5.4)	0-22	**0.014***
	No	38 (18.3)	6.08 (5.3)	0-23	
Neck	Yes	31 (14.9)	9.23 (5.2)	2-22	0.18
	No	177 (85.1)	7.81 (5.4)	0-23	
Chest	Yes	47 (22.6)	8.64 (5.4)	1-23	0.38
	No	161 (77.4)	7.84 (5.4)	0-22	
Back	Yes	64 (30.8)	8.77 (5.5)	1-23	0.19
	No	144 (69.2)	7.69 (5.4)	0-22	
Extent of acne					
≥2 sites	Yes	189 (90.9)	8.25 (5.3)	1-23	0.05
	No	19 (9.1)	5.74 (6.2)	0-20	
≥3 sites	Yes	144 (69.2)	8.18 (5.2)	1-23	0.52
	No	64 (30.8)	7.66 (5.9)	0-20	
≥4 sites	Yes	77 (37.0)	8.12 (4.9)	1-22	0.84
	No	131 (63.0)	7.96 (5.7)	0-23	
Lesion types					0.27
Comedones		14 (6.7)	5.79 (5.1)	0-16	
Inflammatory papules		46 (22.1)	8.00 (5.9)	0-20	
Mixed lesions		148 (71.2)	8.24 (5.3)	1-23	

*A *P* value <0.05 indicates statistical significance.
Abbreviations: DLQI, Dermatology Life Quality Index; SD, standard deviation

had the greatest impact on self-esteem and perceptions across all population groups.[22] It has also been reported that AGA can affect psychological and social experiences as well as QoL, especially in female patients,[23,24] which is similar to our findings. Our investigation determined that AFA with AGA had substantial and statistically significant adverse effects on QoL, especially regarding the choice of clothes and sexual difficulties.

This study has a few limitations. First, the number of patients was insufficient to draw some significant associated factors. In addition, the aggravating factors were subjective, given that patients reported them. Last, evaluating QoL with only 1 tool means that not all aspects of the QoL of the patients may have been captured.

In conclusion, our study demonstrated that AFA had moderate to very large effects on patients' QoL. There was a correlation between the clinical severity of acne and QoL scores. The greatest impacts on QoL were associated with AGA, acne on the perioral area and chin, and patients' perception that their diet aggravated AFA. PCOS and hirsutism did not affect patients' QoL. These data highlight the impact of acne and the associated factors in AFA patients. This underscores the multifaceted nature of adult acne and highlights the need for a holistic approach in understanding and managing this dermatological condition and it presents a compelling avenue for future research and potential interventions to enhance the quality of life for individuals affected by acne.

TABLE 3. Percentage of affected patients and mean score for each aspect of the Dermatology Life Quality Index, compared by the severity of acne, the presence of androgenetic alopecia, and the status of perimenopausal acne.

Aspect of DLQI		Total	Severity of acne*			Androgenetic alopecia			Perimenopausal acne		
		N = 208	Almost clear to mild N = 85	Moderate to severe N = 123	*P* value	Yes N = 12	No N = 196	*P* value	Yes N = 14	No N = 194	*P* value
Symptoms:											
Sore, painful, stinging, itching	Affected patients (%)	166 (79.8)	64 (75.3)	102 (82.9)	0.17	9 (75.0)	157 (80.1)	0.45	10 (71.4)	156 (80.4)	0.30
	Mean score (SD)	1.29 (0.9)	1.12 (0.9)	1.38 (0.9)	0.60	1.33 (1.0)	1.29 (0.9)	0.85	1.00 (0.8)	1.31 (0.9)	0.20
Feelings:											
Embarrassed, self-conscious	Affected patients (%)	182 (87.5)	70 (82.4)	112 (91.1)	0.06	10 (83.3)	172 (87.8)	0.46	12 (85.7)	170 (87.6)	0.55
	Mean score (SD)	1.75 (1.0)	1.53 (1.1)	1.89 (1.0)	**0.012**	2.08 (1.2)	1.72 (1.0)	0.23	1.43 (1.0)	1.77 (1.0)	0.23
Daily activities:											
Limits going shopping, looking after home or garden	Affected patients (%)	132 (63.5)	48 (56.5)	84 (68.3)	0.08	10 (83.3)	122 (62.2)	0.12	9 (64.3)	123 (63.4)	0.95
	Mean score (SD)	1.00 (0.9)	0.80 (0.9)	1.13 (1.0)	**0.011**	1.33 (0.9)	0.98 (0.9)	0.21	0.71 (0.6)	1.02 (1.0)	0.12
Influenced the clothes	Affected patients (%)	87 (41.8)	36 (42.4)	51 (41.5)	0.90	9 (75.0)	78 (39.8)	**0.016**	3 (21.4)	84 (43.3)	0.11
	Mean score (SD)	0.66 (0.9)	0.64 (0.9)	0.67 (0.9)	0.76	1.33 (1.1)	0.62 (0.9)	**0.008**	0.21 (0.4)	0.69 (0.9)	**0.001**
Leisure activities:											
Affected any social or leisure activities	Affected patients (%)	138 (66.3)	52 (61.2)	86 (69.9)	0.19	10 (83.3)	128 (65.3)	0.17	10 (71.4)	128 (66.0)	0.46
	Mean score (SD)	1.13 (1.0)	0.95 (0.9)	1.24 (1.0)	**0.036**	1.67 (1.1)	1.09 (1.0)	0.05	0.93 (0.7)	1.13 (1.0)	0.33
Difficult to do any sport	Affected patients (%)	85 (40.9)	36 (42.4)	49 (39.8)	0.41	7 (58.3)	78 (39.8)	0.17	5 (35.7)	80 (41.2)	0.69
	Mean score (SD)	0.63 (0.9)	0.62 (0.8)	0.64 (0.9)	0.88	1.00 (1.0)	0.61 (0.9)	0.14	0.43 (0.7)	0.65 (0.9)	0.36

TABLE 3. Percentage of affected patients and mean score for each aspect of the Dermatology Life Quality Index, compared by the severity of acne, the presence of androgenetic alopecia, and the status of perimenopausal acne. (Continue)

Aspect of DLQI		Total	Severity of acne*			Androgenetic alopecia			Perimenopausal acne		
		N = 208	Almost clear to mild N = 85	Moderate to severe N = 123	*P* value	Yes N = 12	No N = 196	*P* value	Yes N = 14	No N = 194	*P* value
Work or school:		58 (27.9)									
Difficulties at work or studying	Affected 0patients (%)	.38 (0.7)	24 (28.2)	34 (27.6)	0.93	3 (25.0)	55 (28.1)	0.56	4 (28.6)	54 (27.8)	0.95
	Mean score (SD)		0.38 (0.7)	0.38 (0.7)	0.95	0.50 (0.9)	0.37 (0.7)	0.52	0.43 (0.8)	0.38 (0.7)	0.81
Personal relationships:											
Created problems with partner, close friends, relatives	Affected patients (%)	56 (26.9)	21 (24.7)	35 (28.5)	0.55	4 (33.3)	52 (26.5)	0.41	2 (14.3)	54 (27.8)	0.22
	Mean score (SD)	0.39 (0.7)	0.32 (0.6)	0.45 (0.8)	0.19	0.67 (1.1)	0.38 (0.7)	0.38	0.21 (0.6)	0.41 (0.7)	0.26
Sexual difficulties	Affected patients (%)	13 (6.3)	5 (5.9)	8 (6.5)	0.86	3 (25.0)	10 (5.1)	**0.030**	1 (7.1)	12 (6.2)	0.61
	Mean score (SD)	0.09 (0.4)	0.09 (0.4)	0.09 (0.4)	0.93	0.50 (0.9)	0.67 (0.3)	0.13	0.07 (0.3)	0.09 (0.4)	0.84
Treatment:											
Making home messy, taking up time	Affected patients (%)	91 (43.8)	37 (43.5)	54 (43.9)	0.96	4 (33.3)	87 (44.4)	0.45	6 (42.9)	85 (43.8)	0.94
	Mean score (SD)	0.70 (0.9)	0.62 (0.8)	0.76 (1.0)	0.29	0.58 (1.0)	0.71 (0.9)	0.65	0.71 (0.9)	0.70 (0.9)	0.96

* Severity of acne was evaluated by the Investigator's Global Assessment Scale.
A *P* value <0.05 indicates statistical significance.
Abbreviations: DLQI, Dermatology Life Quality Index; SD, standard deviation

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Conflicts of interest

None declared

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Evaluation of the Efficacy and Safety of the ITM $^{68}Ge/^{68}Ga$ Generator After its Recommended Shelf-life

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ABSTRACT

Objective: ^{68}Ga can be routinely produced by a $^{68}Ge/^{68}Ga$ generator without the need for a cyclotron. It is recommended to replace the $^{68}Ge/^{68}Ga$ generator after 250 elutions or 12 months of shelf-life whichever endpoint is reached first. However, a $^{68}Ge/^{68}Ga$ generator that has gone past its recommended lifespan can still be further used as a ^{68}Ga source for ^{68}Ga-labeled radiopharmaceuticals for use in animal experiments. To ensure the quality of ^{68}Ga eluates, we aimed to evaluate the efficacy and safety of the ITM (Isotope Technologies München) $^{68}Ge/^{68}Ga$ generator in our institute after its recommended shelf-life.

Materials and Methods: A 21-month-old ITM $^{68}Ge/^{68}Ga$ generator was eluted using 4.0 ml of 0.05 M HCl. The ^{68}Ga elution yields were calculated, and ^{68}Ge breakthrough was measured at least 48 h after elution in an aliquot amount using a multichannel analyzer (MCA) with a high-purity germanium probe. Metal impurities in the ^{68}Ga eluates were analyzed by ICP-MS.

Results: The elution yield of ^{68}Ga was 35.2 ± 8.1%; n = 5 (decay corrected). ^{68}Ge breakthrough from the ITM $^{68}Ge/^{68}Ga$ generator was below the detectable level. The average amounts of the metallic ions ^{57}Fe, ^{66}Zn, ^{203}Pb, ^{60}Ni, and ^{63}Cu were 18.60, 9.86, 2.42, 0.52, and 0.47 µg/GBq, respectively.

Conclusion: The ITM $^{68}Ge/^{68}Ga$ generator demonstrated consistent and reliable ^{68}Ga elution profiles with an absence of either ^{68}Ge breakthrough or other metal contaminants in the eluent samples as verified by the manufacturer. The use of the ITM $^{68}Ge/^{68}Ga$ generator could be extended past its recommended shelf-life to prepare ^{68}Ga radiopharmaceuticals that are considered safe and suitable for use in animal experimentation and other applications.

Keywords: $^{68}Ge/^{68}Ga$ Generator; ^{68}Ge Breakthrough; $^{68}Ge/^{68}Ga$ Generator impurities; Gallium-68, $^{68}Ge/^{68}Ga$ Generator shelf-life. (Siriraj Med J 2023; 75: 752-758)

INTRODUCTION

^{68}Ga is a positron-emitting isotope of gallium with a half-life of 68 min. Over the past two decades, ^{68}Ga-labeled tracers have increasingly attracted more attention in diagnostic molecular imaging and clinical research. Due to the nearly ideal nuclear properties of radiometals for positron emission tomography (PET) and chelation chemistry using a bifunctional chelating approach (BFCA)[1], various classes of ^{68}Ga-labeled tracers have been developed, including ^{68}Ga-DOTA-Bombesin[2],

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^{68}Ga-NOTA-RGD[3], ^{68}Ga-albumin[4,5], and ^{68}Ga-DOTA-hEGF (human epidermal growth factor).[6] Moreover, ^{68}Ga was integrated with ^{177}Lu as a twin radiometal for use in a novel theranostic concept.[7] As part of precision medicine, tailor-made ^{68}Ga-based radiopharmaceuticals have been robustly employed in diagnostic prostate cancer imaging, including ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11®)[8,9] and ^{68}Ga-PSMA I&T[10,11], and in diagnosing neuroendocrine tumor imaging, including ^{68}Ga-DOTATATE[12,13], ^{68}Ga-DOTATOC[14,15], and ^{68}Ga-DOTANOC.[16,17] Recently, both ^{68}Ga-PSMA-HBED-CC and ^{68}Ga-DOTATATE were approved by the US FDA for the clinical imaging of prostate cancer and a rare neuroendocrine tumors, respectively. Moreover, a new class of radiotracers based on fibroblast-activation-protein inhibitors (FAPIs) labeled with ^{68}Ga, such as ^{68}Ga-FAPI-04[18] and ^{68}Ga-FAPI-46[19], have demonstrated high tumor-to-background ratios for PET imaging of a wide array of cancers.

^{68}Ga can be produced in an ionic form of the chemically active $^{68}GaCl_3$ by two methods: via a medium-energy cyclotron and a ^{68}Ge/^{68}Ga generator. Cyclotron-produced ^{68}Ga is obtained via ^{68}Zn(p,n)^{68}Ga activation using either a target foil or plate in a solid target[20] or solution in a liquid target.[21] ^{68}Ga production utilizing a solid target results in significantly higher yields. However, the target needs manipulating for the production, including for transferring the solid target into the target holder in the cyclotron. Also, after the bombardment, the solid target has to be removed manually or removed via an automated target transfer system to be dissolved in a hot cell. This manipulating and post-processing can put the personnel at a higher risk of radioactive exposure above the risk they already experience in the cyclotron facility, besides being time-consuming during short half-life ^{68}Ga production. On the other hand, the solution in the liquid target approach can be conveniently loaded into the target holder in the same way as done in ^{18}F production. Also, similar to the solid-target approach, ^{68}Ga must be purified from the remaining ^{68}Zn contaminants in the solution, which leads to a lower yield of ^{68}Ga production.

To overcome these limitations, the ^{68}Ge/^{68}Ga generator is used as an alternative approach and indeed is the most common method to produce ^{68}Ga in clinical use, especially in non-cyclotron medical centers. Commercially available, compact-sized ^{68}Ge/^{68}Ga generators, which reflect the efforts of six decades of development[22], can provide an acidic solution of $^{68}GaCl_3$ that is suitable for routine labeling with BFCA through forming an octahedral coordination complex. A typical generator consists of a small chromatographic column, where ^{68}Ge is immobilized with selected absorbents, such as TiO_2, SnO_2, pyrogallol-derivatized SiO_2, and a mixed matrix, situated in a shielding lead container. ^{68}Ge, a parent radionuclide, spontaneously decays in the column to give ^{68}Ga, with typical yields of 70%–80% in the elution. Secular equilibrium, where both ^{68}Ge and ^{68}Ga have equal radioactivity, in the ^{68}Ge/^{68}Ga generator occurs due to the half-life of ^{68}Ge (270 d) being over 100 times longer than that of ^{68}Ga (68 min). Theoretically, ^{68}Ga accumulated from previous elutions means the system can reach secular equilibrium in around 14 h. Almost 100% ^{68}Ga can be produced after 6 h post elution. Most manufacturers suggest that the ^{68}Ga production cycle for clinical use can be repeated up to 2–3 times a day depending on the generator-loaded radioactivity and the age of the generator.

The first ^{68}Ge/^{68}Ga generator was launched worldwide beginning in the late 1990s. Some of its many advantages that deserve mentioning include the stable column matrices, easy elution, long shelf-life of 1–2 years, effective shielding container, and compact size. Each ^{68}Ge/^{68}Ga generator manufacturer offers various parameters in terms of different types of column matrix, molarity of the HCl eluent, ^{68}Ga volume of elution, ^{68}Ge breakthrough and impurity amount, and weight of the generator, as shown in Table 1.

Although it is necessary to replace a new ^{68}Ge/^{68}Ga generator for clinical use after its recommended shelf-life, the "expired" ^{68}Ge/^{68}Ga generator can actually continue to be employed to elute ^{68}Ga to label certain ^{68}Ga-based radiopharmaceuticals for research purposes, especially for animal experimentation. In the present study, the essential parameters of an over-lifespan ITM ^{68}Ge/^{68}Ga generator (i.e., used past its recommended lifespan) were evaluated to ensure its efficacy and safety for continuing ^{68}Ga elution.

MATERIALS AND METHODS

A SiO_2-based ^{68}Ge/^{68}Ga generator was purchased from Isotope Technologies München (ITM) Medical Isotopes GmbH, Germany (previously, Isotope Technologies Garching (ITG)). All the solvents and reagents were purchased from commercial suppliers and used without further purification. 0.05 M HCl (GMP) was purchased from ABX Advanced Biochemical Compounds.

The ^{68}Ga activity was measured with a dose calibrator (CRC25R, Capintec, USA). The ^{68}Ge activity was measured by gamma-ray spectrometry using a multichannel analyzer, A multichannel analyzer (MCA) integrated gamma spectrometer system (Ortec DSPEC jr 2.0) coupled with a high-purity germanium probe (HPGe probe, Ortec Gem20P4-70) was used in the experiments. The

TABLE 1. Characteristics of some commercially available $^{68}Ge/^{68}Ga$ generators.

Company	Generator specifications					
	Column material	Eluent	^{68}Ge breakthrough	Elution volume	Metallic impurities	Weight of generator
Eckert & Ziegler Cyclotron Co. Ltd. (Obninsk)[23]	TiO_2	0.1 M HCl	< 0.005%	5 ml	Ga < 1 µg/mCi Ni < 1 µg/mCi	11.7 kg
Eckert & Ziegler IGG100 and IGG101 GMP (Gallia Pharm)[23]	TiO_2	0.1 M HCl	< 0.001%	5 ml	Fe < 10 µg/mCi Zn < 10 µg/mCi	IGG100 = 10 kg IGG101 = 14 kg
iThemba LABS, South Africa[23]	SnO_2	0.6 M HCl	< 0.002%	5 ml	1–20 ppm for Sn, Fe, Cu, Mn, and Al	
Pars Isotope (PARS-GalluGEN®), Tehran, Iran[23]	SnO_2	0.6 M HCl	< 0.00002%		>1 ppm for Fe, Sn and Zn	
IRE EliT (Galli Eo®), Fleurus, Belgium[23]	Unspecified	0.1 M HCl	< 0.001%		< 10 µg/GBq of ^{68}Ga for Fe, Cu, Ni, Zn, Pb, and Al	
Isotope Technologies Garching, GmbH, Germany[23]	Silica gel modified with dodecayl gallate	Sterile 0.05 M HCl	< 0.005%	3–4 ml	< µg/GBq of ^{68}Ga for (Ni, Zn, Nb, Pb, Fe, and Cu)	
Isotope ROSATOM[24]	TiO_2	0.1 M HCl	< 0.005%	5 ml		11.7 kg
I.D.B. Holland B.V.[25]	SnO_2	0.6 M HCl	< 0.002%	6 ml	< 10 ppm (Ga, Ge, Zn, Ti, Sn, Fe, Al, and Cu)	26 kg

metal-ion impurities in the ^{68}Ga eluates were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS).

Evaluation of 68Ga elution

A 21-months-old $^{68}Ge/^{68}Ga$ generator (Isotope Technologies München (ITM) Medical Isotopes GmbH, Germany) loaded at the manufacturer site with ^{68}Ge 50 mCi was used for the study evaluation. Before starting the experiments, the generator was eluted with 30 ml of 0.05 M HCl to wash away ^{68}Ge breakthrough and other impurities accumulated in the pyrogallol-formaldehyde resin column as recommended by the manufacturer because the system had not been used for several months. The ITM $^{68}Ge/^{68}Ga$ generator was manually eluted with 4.0 ml of 0.05 M HCl. Subsequently, the elution profile was studied by collecting the eluates in fractions of 1 ml for 4 fractions. The elution yield of ^{68}Ga activity in each fraction was immediately determined in a dose calibrator.

^{68}Ge breakthrough measurement

^{68}Ge breakthrough was measured after the separated ^{68}Ga eluates were allowed to decay for at least 48 h to a level where the ^{68}Ge activity could be indirectly detected as a decay product. All the eluates were measured under the following conditions: constant geometry using 1.5 ml, placed at a distance of 10 cm from the detector, and then all the decayed samples were counted to determine ^{68}Ge breakthrough with a measuring time of 1,000 sec per fraction and with a dead time of less than 10%. Due to the half-life of ^{68}Ge being much longer than that of ^{68}Ga, the activity of ^{68}Ga was theoretically calculated by using the secular equilibrium equation[26] (Equation 1):

$$A^t_{Ga} = A^0_{Ge} = (1\text{-}e^{(\ln 2/t_{1/2})t}) \quad \text{(Equation 1)}$$

where A^t_{Ga} and A^0_{Ge} are ^{68}Ga activity at time points t after elution and ^{68}Ge activity when co-eluted (i.e., at breakthrough), and $\lambda = \ln 2/t_{1/2}$

The percentage of ^{68}Ge-breakthrough in all the samples should be lower than 0.005%. (According to the generator specification and $^{68}GaCl_3$ monograph.)

Metal impurities measurement

The potential metal-ion impurities in the ^{68}Ga eluates were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) after the fractionated ^{68}Ga eluates had been allowed to decay for at least 48 h. The trace metals of interest were ^{57}Fe, ^{60}Ni, ^{63}Cu, ^{66}Zn, and ^{208}Pb measured as contaminants per elution and per fraction. The operating conditions for the ICP-MS during the measurements were as follows: plasma power, 1550 W; cool flow, 14 L/min; auxiliary flow, 0.8 L/min; nebulizer flow, 1.043 L/min; helium flow, 0 ml/min; sampling depth, 5 mm; spray chamber temp, 2.7 °C; and pump speed, 40 rpm.

To determine the contents of these metals, calibration standards containing these elements in the following concentration were prepared to obtain a concentration series for the calibration curve: 1, 10, 50, and 100 ppb. The generator eluent was diluted by a factor of 5 with 0.05 M HCl. The 0.05 M HCl was further measured as the blank sample.

Results and Discussion

Generator elution and elution yield

At 21 months after its last calibration date, the GMP-certified ITM ^{68}Ge/^{68}Ga generator contained 10.643 mCi of ^{68}Ga. The elution yield of ^{68}Ga was 35.2 ± 8.1%; n = 5 (decay corrected), ranging from 28.6% to 44.3%. The elution yield decreased with a linear trend in a similar pattern to in a previous report (R2 = 0.957)[27] over the course of the study. The majority of the ^{68}Ga activity was found in fractions 2 to 4. The elution profiles of each eluate are shown in Fig 1. Slightly different elution profiles were observed with the activity eluted in fractions 2–3 compared to in fractions 2–4 at the beginning time of the generator operation.

^{68}Ge breakthrough measurement

^{68}Ge breakthrough is expressed as a percentage of ^{68}Ge activity on the elution day relative to ^{68}Ga activity at calibration time. In this study, ^{68}Ge breakthrough from the ITM ^{68}Ge/^{68}Ga generator could not be detected as the minimal sensitivity of the HPGe probe was 10-5%. However, a previous report by Chakravarty et al mentioned that the ^{68}Ge breakthrough of a SiO_2-based ^{68}Ge/^{68}Ga generator was always <10^{-3}% over the period of 1 year.[27]

^{68}Ge was strongly absorbed on the pyrogallol-formaldehyde resin column. The breakthrough of ^{68}Ge in all the samples was below the detectable level over the extended periods of generator usage (lower than 0.005% according to the generator specification and $^{68}GaCl_3$ monograph). According to the recommendation of a monograph of the European Pharmacopeia, the limitation for ^{68}Ge breakthrough could be high as >100 times the safety level for patients.[28] The decreased percentage ^{68}Ge breakthrough (down to 0.0012%) showed the beneficial characteristics of the ITM generator, which could be extrapolated to an overall decrease in radiolysis.[29] Therefore, the level of ^{68}Ge breakthrough from the ITM ^{68}Ge/^{68}Ga generator after its recommended shelf-life was considered acceptable for both basic research as well as animal imaging research.

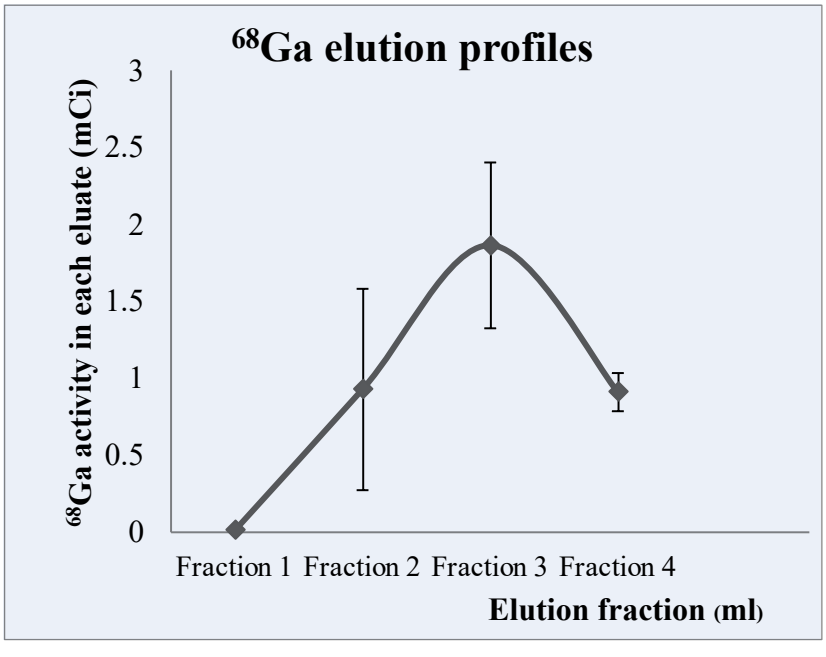

Fig 1. ^{68}Ga elution profiles of a 21-month-old ITM ^{68}Ge/^{68}Ga generator after its recommended shelf-life.

Metal impurities

The common chemical impurities of concern in ^{68}Ga elution are the metallic ions Fe, Zn, Pb, Ni, and Cu. These metal impurities are generally expressed in mg/l (ppm). The average amounts of the metallic ions Fe, Zn, Pb, Ni, and Cu found in this study were 18.60, 9.86, 2.42, 0.52, and 0.47 µg/GBq, respectively. The analysis results for the metal impurities are shown in Table 2. Although the excess amount of Fe^{3+} (approximately 8 µg/GBq) in the eluent from the over-lifespan ITM ^{68}Ge/^{68}Ga generator could potentially compete with ^{68}Ga during complex formation[30,31] to reduce the radiochemical yield (RCY), the calculated radioactivity of the final product here was more than 0.3 mCi (1.1 MBq), which was still enough for use in animal experiments and studies.[32] Moreover, the Fe^{3+} residue can be removed in a purification step by reversed-phase Sep-Pak (C-18). Therefore, the radiochemical purity (RCP) of the final product can be obtained in the same quality as required for use in clinical practice.

Other metallic ions, such as Pb, Cu, and Ni, were found in amounts of less than 10 µg/GBq according to the eluate specification. Since the ITM generator employed a modified dodecyl-3,4,5-trihydroxybenzoate hydrophobically bound to an octadecyl-modified silica resin, which allows its authorized marketing in Europe as a pharmaceutical-grade generator[29], the other metallic contents of the eluate were found to be extremely low.

TABLE 2. Analysis of the metal impurities in the ^{68}Ga eluate using inductively coupled plasma-mass spectrometry (ICP-MS)

	^{57}Fe (ppm)	^{60}Ni (ppm)	^{63}Cu (ppm)	^{66}Zn (ppm)	^{208}Pb (ppm)
1	5.893	0.198	0.027	4.173	1.274
	4.463	0.070	0.096	7.920	1.944
	4.390	0.060	0.086	0.969	0.206
	4.294	0.064	0.057	1.015	0.434
2	5.682	0.189	0.234	13.343	0.403
	4.955	0.111	0.130	1.159	0.369
	4.627	0.085	0.109	0.996	0.328
	4.326	0.068	0.093	0.941	0.465
3	4.435	0.167	0.114	2.910	0.258
	4.413	0.076	0.082	1.042	0.245
	4.213	0.072	0.118	0.973	0.332
	4.227	0.123	0.114	1.246	0.247
4	4.525	0.177	0.145	1.622	0.759
	4.540	0.152	0.107	1.138	0.326
	3.932	0.148	0.114	1.115	0.221
	4.347	0.123	0.133	0.990	0.180
5	5.415	0.276	0.129	3.184	0.251
	5.850	0.192	0.174	2.286	3.679
	4.261	0.124	0.168	1.090	0.074
	4.178	0.136	0.114	1.207	0.106

CONCLUSION

The manufacturer's recommended lifespan for the pyrogallol-formaldehyde resin-based $^{68}Ge/^{68}Ga$ generator produced by ITM GmbH Germany is 12 months or 250 elutions; however, it still provides an adequate amount of ^{68}Ga eluent that could be effectively used to prepare ^{68}Ga-radiopharmaceuticals for basic research after 21 months, long past its recommended shelf-life. The ITM $^{68}Ge/^{68}Ga$ generator demonstrated consistent and reliable ^{68}Ga elution profiles with the absence of ^{68}Ge breakthrough in the eluant samples as verified by the manufacturer. Even though free Fe ions were found in an excess amount of 18 μg/GBq, which can affect the RCY, the radioactivity in the final product was still enough for animal experiments and studies. The other metallic ions Zn, Pb, Ni, and Cu, except Fe, were all less than 10 μg/GBq as indicated in the manufacturer's specification. Therefore, the ITM $^{68}Ge/^{68}Ga$ generator has enhanced use beyond its recommended shelf-life to prepare ^{68}Ga radiopharmaceuticals that are considered safe and suitable for further animal experiments and studies.

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Conflict of interest: All authors declare that they have no conflicts of interest.

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Efficacy of Oral Iron Supplementation in Treating Patients with Female Pattern Hair Loss and Low Serum Ferritin: A Pilot Study

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To the Editor: Androgenetic alopecia or pattern hair loss (PHL) is the most common cause of non-scarring alopecia in the general population. It is characterized by a gradually progressive decline in hair density and diameter in both sexes.[1] The association between iron deficiency (ID) and hair loss is controversial.[2] Currently, there is no standard oral iron supplementation for patients with Female PHL (FPHL) who have ID. We investigated the efficacy of oral iron supplementation for treating FPHL patients with ID.

Patients diagnosed with FPHL and ID (serum ferritin level <70 μg/l) were included in the study.[3] The FPHL diagnoses were made by dermatologists based on histories, physical examinations, and dermoscopic findings.[4] We excluded patients with other hair diseases (e.g., scarring alopecia, telogen effluvium), scalp inflammatory diseases (e.g., scalp psoriasis, tinea capitis), and systemic diseases that can have an impact on hair loss conditions (e.g., diabetes mellitus, hypo/hyperthyroidism). Patients who had received any other type of hair-thinning treatment in the prior 24 weeks were also excluded.

We performed a 24-week, randomized, open comparative study at a dermatology clinic, Siriraj Hospital, Mahidol University. Twenty individuals were recruited and assigned to two groups of 10 by using block randomization. The treatment group was given 200 mg ferrous sulfate (65 mg elemental iron; Inpac Pharma Co. Ltd., Bangkok, Thailand) orally three times daily after meals, as well as 3% topical minoxidil solution (made by the Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University). 50% ethyl alcohol, 25% propylene glycol, and 25% filtered water were used as solution vehicles. Patients were instructed to apply 1 ml of minoxidil twice daily to affected areas of the scalp. The control group was administered 3% minoxidil solution alone, with the same instructions and treatment period.

The primary outcome was a change in terminal hair density (hairs/cm^2) of the target area on the scalp vertex was evaluated from baseline to week 24. Secondary outcomes were global photographic assessments (by two blinded dermatologists), patient satisfaction, and change in serum ferritin and CBC.

Seventeen patients completed the study. Dropouts were unrelated to treatment side effects. Their mean age was 35.2 years, and most (70.6%) had Ludwig grade II. There were no significant differences in the profiles of the two groups, except baseline serum ferritin (Table 1). Consequently, the serum ferritin level was adjusted using multiple linear regression to diminish the baseline difference. The changes in hair densities of the groups were not significant ($P = 0.118$). At week 24, there were no significant differences in physician assessment and patient satisfaction between the groups (Table 2). Side effects reported from iron supplements were dark stools (35.3%), diarrhea (17.6%), nausea (11.8%), gastrointestinal irritation (11.8%), and constipation (11.8%).

Serum ferritin, a main iron-binding protein in nonerythroid cells that decreases in the very early stage of ID, is considered the most effective screening tool for ID.[5] Park and colleagues administered an oral iron

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TABLE 1. Demographic data, baseline clinical characteristics, and laboratory results of patients with female pattern hair loss and iron deficiency.

	Total (N = 17)	Ferrous sulfate and 3% minoxidil solution (N = 9)	3% minoxidil solution (N = 8)	*P* value
Age (years), mean ± SD	35.2 ± 7.4	34.1 ± 6.5	36.5 ± 8.7	0.527
Duration of hair loss (months), median (min, max)	12.0 (2.0, 120.0)	12.0 (4.0, 84.0)	12.0 (2.0, 120.0)	0.618
Comorbidities, n (%)				
Allergic rhinitis	2 (11.8)	0	2 (25.0)	0.206
GERD	1 (5.9)	0	1 (12.5)	0.471
Family history of hair loss, n (%)	9 (52.9)	5 (55.6)	4 (50.0)	1.000
Physical examination				
Ludwig classification, n (%)				
Grade I	4 (23.5)	1 (11.1)	3 (37.5)	0.424
Grade II	12 (70.6)	7 (77.8)	5 (62.5)	
Grade III	1 (5.9)	1 (11.1)	0	
Signs of hyperandrogenism, n (%)	6 (35.3)	3 (33.3)	3 (37.5)	1.000
Hirsutism	2 (11.8)	1 (11.1)	1 (12.5)	1.000
Acne vulgaris	4 (23.5)	2 (22.2)	2 (25.0)	1.000
Oily skin	3 (17.6)	2 (22.2)	1 (12.5)	1.000
Irregular menstruation	2 (11.8)	1 (11.1)	1 (12.5)	1.000
Hair density, mean ± SD	98.9 ± 36.8	114.8 ± 40.9	81.1 ± 22.4	0.057
Laboratory investigations				
Serum ferritin (µg/l), mean ± SD	39.2 ± 19.6	23.9 ± 11.8	56.4 ± 8.9	**< 0.001***
Hemoglobin (g/dl), mean ± SD	12.8 ± 0.7	12.7 ± 0.8	12.9 ± 0.7	0.578
Hematocrit (%), mean ± SD	38.9 ± 2.3	39.1 ± 2.6	38.9 ± 2.0	0.959
ESR (mm/h), median (min, max)	11.0 (7.0,42.0)	9.0 (7.0,25.0)	15.5 (7.0,42.0)	0.091
25-hydroxyvitamin D_2 (ng/ml), mean ± SD	23.9 ± 5.1	24.6 ± 4.5	23.3 ± 5.8	0.728

*, *P* value < 0.050

Abbreviations: ESR, erythrocyte sedimentation rate; GERD, gastroesophageal reflux disease; SD, standard deviation

TABLE 2. Clinical evaluations and laboratory results of patients with female pattern hair loss and iron deficiency after treatment.

		Mean ± SD or n (%) Ferrous sulfate and 3% minoxidil solution (N = 9)	3% minoxidil solution (N = 8)	*P* value
Clinical evaluations				
Change in terminal hair density (hairs/cm^2), mean ± SD	Difference (baseline VS week 24)	20.6 ± 16.7	20.6 ± 24.1	0.995
Physician assessment	At week 24			
Improvement		4 (44.4)	6 (75.0)	1.000
No improvement		5 (55.6)	2 (25.0)	
Patient satisfaction	At week 24			
Satisfied		8 (88.9)	7 (87.5)	1.000
Not satisfied		1 (11.1)	1 (12.5)	
Laboratory investigations				
Serum ferritin (µg/l), mean ± SD	Difference (baseline VS week 24)	94.5 ± 59.5	4.7 ± 13.2	**0.003***
Hemoglobin (g/dl), mean ± SD	Difference (baseline VS week 24)	0.09 ± 0.52	0.09 ± 0.41	0.995
Hematocrit (%), mean ± SD	Difference (baseline VS week 24)	0.13 ± 1.84	0.30 ± 1.55	0.844

*, *P* value < 0.050
Abbreviation: SD, standard deviation

supplement (325 mg of ferrous sulfate twice daily; 65 mg elemental iron) for 6 months to FPHL patients with serum ferritin <70 µg/l. There was no significant difference in the patient-assessed treatment responses of the supplementation and non-supplementation groups.[6] Moreover, Sinclair reported that four of seven FPHL patients with serum ferritin <20 µg/l responded to oral spironolactone and iron replacement, with a similar response rate to FPHL patients with normal ferritin treated with oral spironolactone alone.[2] Although the total elemental iron prescribed in our study was higher than those in previous studies, treatment responses (terminal hair density, physician assessment, and patient satisfaction) were not statistically significant compared with topical 3% minoxidil treatment alone.[2,6]

In conclusion, topical 3% minoxidil combined with oral iron supplementation was not superior to topical 3% minoxidil alone in treating FPHL with ID. However, no serious side effect was documented from that supplement. Further studies with larger samples are needed to determine the efficacy of oral iron supplementation for FPHL with ID.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions

DT, NJ, CS and CL conceptualized this study, generated population and conducted the field trials with assistance from KT, RT and SV. DT and SW performed the data analysis with advice from KT, RT and SV. DT, KT, SW and NV wrote the manuscript. All authors revised the manuscript.

Disclosures

All named authors have nothing to disclose.

Compliance with Ethics Guidelines

This study is approved by the Siriraj Institutional Review Board with Certificate of Approval No. Si 500/2015

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflict-of-interest declaration

All authors declare that there are no conflicts of interest related to any aspect of this research.

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