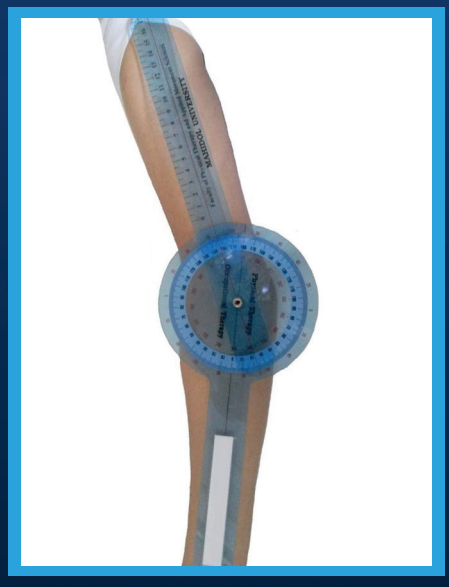
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The Contribution of Outdoor Fine Particulate Matter to Indoor Air Quality in Bangkok Metropolitan Region, Thailand – Are Indoor Dwellers Safe?

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ABSTRACT

Objective: This study aimed to analyze the relationship between indoor and outdoor fine particulate matter (PM2.5) concentrations and to characterize factors that may contribute to domestic PM2.5 concentrations, including smoking, printer/copier, and cooking activities.

Methods: We measured the ambient and indoor PM2.5 concentrations from 7 sampling sites in Bangkok Metropolitan and vicinity area, Thailand by using PM2.5 concentrations sensor (SN-GCHA1, Panasonic Photo & Lighting Co., Ltd). Real-time PM2.5 concentrations, temperature, and relative humidity (RH) measurements were recorded hourly for two consecutive days during February 20th to March 2nd, 2018. We collected real-time indoor and outdoor PM2.5 mass concentrations at the same time. Factors influencing domestic PM2.5 production in the indoor environment were recorded.

Results: The mean indoor PM2.5 concentrations from each site ranged from 20.05-45.85 μg/m^3 and the mean outdoor PM2.5 concentrations ranged from 9.42-56.56 μg/m^3. The ambient and indoor PM2.5 mass concentrations curves tended to fluctuate in a similar trend. There was a significantly positive correlation between the average ambient and the average indoor PM2.5 mass concentrations in all studied places. The correlation coefficient (r) varied from 0.6 to 0.833. Five from seven sites demonstrated a strong correlation ($r \geq 0.7$), whereas, two from seven sites demonstrated a moderate correlation ($0.5 \leq r < 0.7$). The average indoor/ambient PM2.5 concentration ratio from each place ranged from 0.37 to 3.57.

Conclusion: The indoor PM2.5 concentrations are correlated with the ambient PM2.5 concentrations. The concentrations of PM2.5 in most sampling sites were higher than the recommended threshold. Hence, indoor dwellers are still at risk for health impacts from PM2.5. Besides public management of the ambient PM2.5, the interventions dealing with the indoor PM2.5 should be promoted concurrently.

Keywords: Particulate matter; PM2.5; indoor air pollution; allergic rhinitis; asthma (Siriraj Med J 2018;70: 265-271)

INTRODUCTION

With fast urban development and modernization, air pollution is rapidly worsening globally, especially in low- and middle-income countries. Major air pollutants include gaseous pollutants (i.e. O_3, NO_2, SO_2) and particulate matters (i.e. PM10, PM2.5).[1] In Thailand, with growing number of factories and combustion sources, the population-attributable fraction of the disease burden for all-causes mortality in adults due to PM2.5 was one of the highest among all air pollutants up to 7.5%.[2]

PM2.5 is fine particulate matter with aerodynamic diameter less than 2.5 micrometers. The primary

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contributors of PM2.5 are mainly from the traffic and industry, including fuel combustion from power plant, oil refinery, and automobiles. Due to its small size compared to larger particles, PM2.5 can reach the smallest airways and alveoli, causing serious effects on human health.[3] Based on numerous epidemiological evidences, PM2.5 has been considered as the main culprit of the adverse cardiovascular effects of air pollution on human health. PM2.5 exposure was associated with increased risk of incident stroke.[4] Higher long-term fine particulate matter concentrations are associated with increased carotid intima-media thickness (IMT) progression and that greater reduction in fine particulate matter concentrations are related to slower IMT progression.[5] Some reports also suggested the potential relationship between air pollution and various cancers. Higher levels of ambient PM2.5 concentrations were associated with an increment in lung cancer mortality.[6] PM2.5 concentrations was also correlated with increased risk of mortality for specific cause of cancer in upper digestive tract and in digestive accessory organs.[7]

A number of studies found the relationship of level of PM2.5 and allergic disease. In mouse model, mice with allergic rhinitis showed elevated levels of adhesion molecules and inflammatory cytokine expressions as well as nasal remodeling after exposure to PM2.5.[8,9] PM2.5 was found to adjunct the pollen in promoting allergic disease. The higher level of PM2.5, the greater pollen effect was detected.[10] The prevalence of allergic rhinitis was significantly associated with PM2.5 concentrations.[11,12] Furthermore, increase in PM2.5 was correlated with emergency room visit due to acute exacerbation and other acute respiratory disease in patients with chronic respiratory disease, especially in children.[13-15] Hence, management of PM2.5 should be considered to be crucial in treatment and prevention of allergic disease.

WHO Air quality guidelines (AQGs) in 2016 recommended the threshold level for PM2.5 concentrations at below 10 μg/m^3 for annual mean and below 25 μg/m^3 for the 24-hour mean. However, no threshold has been identified below which no damage to health is demonstrated. Therefore, the AQGs suggested achieving the lowest concentrations of PM as possible.[1]

Most studies are limited only to ambient particulate matter concentrations, while most urban residents spend more than 80% of daily life indoors.[14] Therefore, exposure to airborne particulate matter primarily occurs indoors. As ambient particulate matter penetrates from outdoor environment to indoors through ventilation systems and building leaks, research interest has been focused on the relationship between indoor and outdoor particulate matter concentrations in various settings. In China, 24-hour real-time indoor and ambient PM2.5 concentrations and indoor/ambient PM2.5 ratio (I/A ratio) were measured. I/A ratio was used for evaluation of how easy the indoor environment can be influenced by outdoor PM2.5 and examined the impacts of indoor sources on indoor PM2.5 mass concentrations. Hourly ambient PM2.5 concentrations had a median of 58 microgram/m^3 while hourly indoor PM2.5 had a median of 34 microgram/m^3. The median I/A ratio was 0.62.[13] There was a variation of I/A ratio from different studies. This could be due to the differences in the outdoor pollution, outdoor weather, indoor sources of pollution, the building envelope itself, and the air changes per hour.[16] The I/A ratios for all air pollutants are lowest in buildings with closed windows, compared to ventilated environments.[17]

Although in Thailand, especially Bangkok Metropolitan Area, where serious air pollution problems have occurred for decades, no study has been conducted to study the relationship of indoor and ambient air pollution in different ventilation conditions. This study was designed to assess the indoor and ambient fine particulate matter (PM2.5) concentrations in different ventilation conditions (open and closed ventilation systems) in different building categories, i.e. residential houses, hospital, office buildings, condominiums in Bangkok Metropolitan Area. Our objectives were to analyze the relationship between indoor and outdoor PM2.5 concentrations and to characterize factors that may contribute to endogenous PM2.5 concentrations, including smoking, printer/copier, and cooking activities.

MATERIALS AND METHODS

Sampling sites and sampling period

The study was conducted in 7 sampling sites in Bangkok Metropolitan and vicinity area, Thailand – including Bangkok, Nonthaburi, Nakhon Pathom, Samutprakarn provinces (Fig 1). Sampling sites were divided into 4 categories, which were offices, residential houses, hospitals, and high-rise accommodations (i.e. hotels/condominiums). Hourly real-time PM2.5 concentrations, temperature, and relative humidity (RH) measurements were recorded for two consecutive days during February 20th to March 2nd, 2018. We collected real-time indoor and outdoor PM2.5 mass concentrations at the same time. We excluded the days on which raining occurred because this might affect the PM2.5 mass concentration level, RH, temperature, and the comparisons of data.

There were three different ventilation conditions for each site. Sensors were located at the ambient environment, indoor environment with a closed ventilation system,

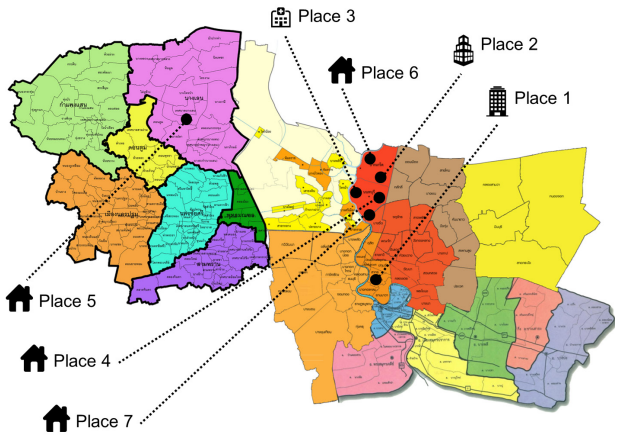


Fig 1. Map of sampling sites.

where all doors and windows were tightly closed all day, and indoor environment with an open ventilation system, all doors are closed, but windows were kept partially opened for the entire sampling period. We also calculated I/A ratio which was defined as a ratio between indoor PM2.5 mass concentrations compared with ambient PM2.5 mass concentrations. In order to reflect the real situation for office indwellers in Bangkok, we used the indoor PM2.5 concentrations measured in the closed ventilation setting to calculate I/A ratio.

For the ambient environment, sensors were placed on the ground 1.5 meters away from the building. For the indoor environment, sensors were placed in the middle of the room, at the level of the breathing zone of a sitting person (1.5 meters above the floor). Factors influencing PM2.5 endogenous production in the indoor environment were recorded. These include smoking activities, printer and/or copier, cooking activities, and proximity to traffic area.

Instrumentation and data collection

All sensors, including PM2.5 concentrations sensor (SN-GCHA1, Panasonic Photo & Lighting Co., Ltd), a temperature sensor (RHHI-112A, Shinyei Technology Co, Ltd), and RH sensor (RHHI-112A, Shinyei Technology Co, Ltd), were placed within one control box (9 cm x 16 cm x 11 cm). The measurement complied with Federal Reference Method (FRM) according to the recommendation from US. EPA. Data recorded by these sensors at each measurement site were transferred through Wi-Fi connection to the local router, and from the local router to cloud server through 4G internet connection. Hourly real-time data of indoor and ambient PM2.5 concentrations, temperature, and RH were exported in Excel files for statistical assessment.

Statistical analysis

All statistics were analyzed by using SPSS version 18.0. Ambient and indoor PM2.5 concentrations were shown as mean, median, SD, and 25th and 75th percentile. The correlation between ambient and indoor PM2.5 concentrations was demonstrated by simple linear regression analysis. Comparison of PM2.5 concentrations and I/A ratios in multiple places with different factors which influenced endogenous PM2.5 production in indoor environment (i.e. whether smoking was allowed or prohibited, having printer or not, and cooking activities was allowed or not) was performed by t-test or Mann Whitney U Test. P values of less than 0.05 ($p < 0.05$) were considered as statistically significant.

RESULTS

Data from 7 sampling sites were systematically collected. Factors influencing indoor PM2.5 concentrations were recorded and summarized in Table 1. Five from seven sampling sites (71%) included at least one printer and/or copier in the room. Four from seven sites (57%) had cooking activities present in indoor environment, and two from seven sites (28%) had smoking activities present inside the building.

The Concentrations of Ambient and Indoor PM2.5

The distribution of PM2.5 mass concentrations from seven sampling sites during two consecutive days was demonstrated in Fig 2. During data collection, the hourly mean ambient temperatures were 28.8-35.2°C. The minimal and maximal ambient temperatures were 24.8°C and 41.6°C, respectively. The hourly indoor temperatures were in the range of 25.4-31.3°C, whereas the minimal and maximal indoor temperatures were 23.3°C and 35.3°C, respectively. The mean RH was 55.2-63.1% for indoor, and 60.2-72.6% for outdoor.

All places had diurnal changes of PM2.5 mass concentrations. However, the ambient and indoor PM2.5 mass concentrations curves tended to fluctuate in the similar trend. Ambient PM2.5 mass concentrations were higher than the indoor PM2.5 mass concentrations in most sampling sites, except place 1 and place 6. The mean indoor PM2.5 mass concentrations from each site ranged from 20.05-45.85 μg/m^3 and the mean outdoor PM2.5 mass concentrations ranged from 9.42-56.56 μg/m^3. In contrast, the average PM2.5 mass concentrations from all sites was 28.6 μg/m^3 for indoor and 32.5 μg/m^3 for outdoor. We demonstrated the mean PM2.5 mass concentrations from seven sampling sites in Fig 3.

TABLE 1. Factors influencing indoor PM2.5 concentrations in sampling sites.

Place No.	Area	Building Category	Smoking		Printer and/or Copier		Cooking	
			Yes	No	Yes	No	Yes	No
1	Silom - Bangkok	High-rise accommodation	√		√		√	
2	Chaengwatta - Nonthaburi	Office building	√		√		√	
3	Sanambin Nam - Nonthaburi	Hospital		√	√			√
4	Ngamwongwan - Nonthaburi	Residential house		√		√		√
5	Bang Len - Nakhon Pathom	Residential house		√		√	√	
6	Bang Phut - Nonthaburi	Residential house		√	√		√	
7	Talat Kwan - Nonthaburi	Residential house		√	√		√	

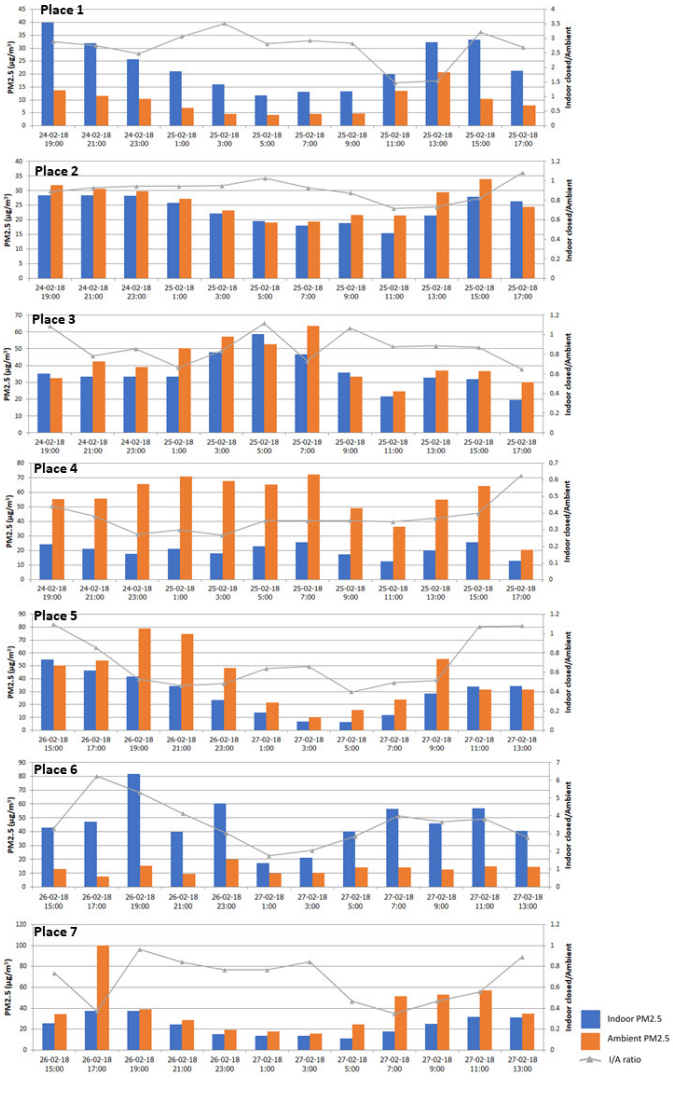


Fig 2. Daytime diurnal variation of PM2.5 mass concentrations from 7 different places in Bangkok Metropolitan Area.

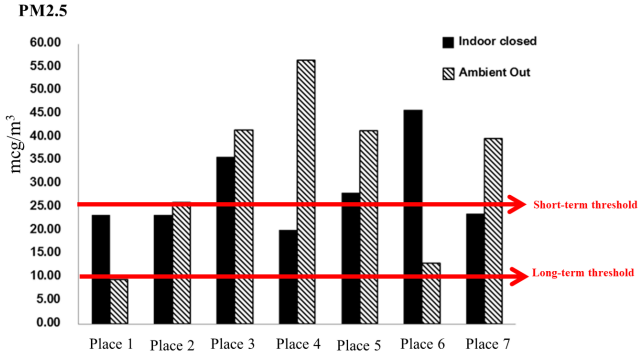


Fig 3. Average PM2.5 concentrations from 7 different places in Bangkok. The horizontal line indicates WHO threshold of PM2.5 concentrations for short-term exposure (25 μg/m^3) and long-term exposure (10 μg/m^3).

Ambient and indoor PM2.5 mass concentration relationship

We summarized the descriptive statistics of outdoor and indoor PM2.5 mass concentrations in Table 2. The average I/A ratio from each place ranged from 0.37 to 3.57. There was a significantly positive correlation between the average ambient and average indoor PM2.5 mass concentrations in all measurable places. The correlation coefficient (r) varied from 0.6 to 0.833. Five from seven sites demonstrated a strong correlation ($r \geq 0.7$), whereas, two from seven sites demonstrated a moderate correlation ($0.5 \leq r < 0.7$).

Stratification by Factors Influencing Endogenous PM2.5 Production

Each sampling site had different factors which were involved in the endogenous production of indoor PM2.5. The presence or absence of such factors was stratified to

TABLE 2. Correlation of indoor (closed ventilation system) and ambient PM2.5 concentrations using simple linear regression (r, correlation coefficient; beta, regression coefficient; SE, standard error; R^2, Coefficient of determination), analyzed by simple linear regression.

Place	Indoor PM2.5 concentrations (µg/m³)					Ambient PM2.5 concentrations (µg/m³)					r	Beta	SE	R^2	*P*-value
	Mean	SD	Median	P25	P75	Mean	SD	Median	P25	P75					
1	23.30	9.28	25.68	18.30	35.01	9.42	5.02	29.18	14.65	50.32	0.77	1.41	0.376	0.586	0.004
2	23.37	4.67	21.15	14.67	32.12	26.02	5.11	9.09	4.63	12.53	0.83	0.76	0.160	0.694	0.001
3	35.78	10.86	23.94	19.23	27.99	41.58	11.92	25.82	21.55	30.23	0.80	0.73	0.174	0.634	0.002
4	20.05	4.43	33.36	32.33	41.08	56.56	15.29	37.98	32.90	51.45	0.75	0.22	0.061	0.556	0.005
5	28.04	15.93	20.81	17.66	23.74	41.40	22.41	60.04	52.10	66.80	0.73	0.52	0.155	0.527	0.008
6	45.85	17.23	31.32	12.77	38.07	12.99	3.31	40.15	22.72	54.71	0.60	3.13	1.319	0.360	0.039
7	23.64	9.41	44.36	39.98	56.69	39.70	23.64	13.54	10.05	14.74	0.68	0.27	0.091	0.473	0.013

compare the median I/A ratio (Fig 4). The places where indoor smoking was allowed had statistically significant higher I/A ratio than where smoking was prohibited ($p = 0.001$). The places where printers were present had significantly higher I/A ratio than where a printer was not present ($p < 0.001$). I/A ratio was also found to be significantly higher in the places where cooking was allowed, compared with the places where cooking was not allowed ($p < 0.001$).

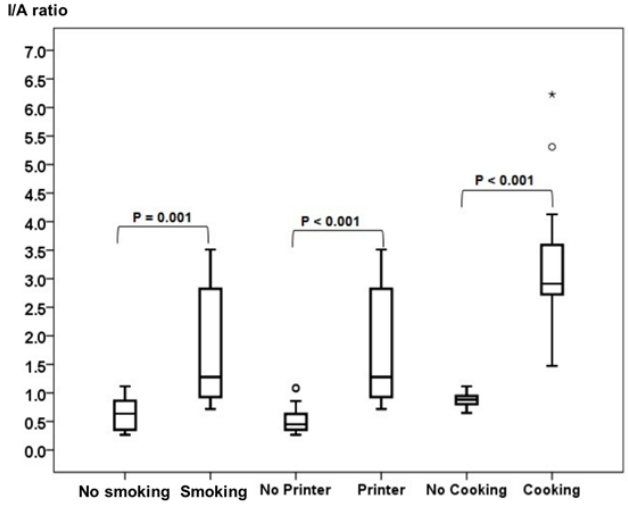


Fig 4. Median I/A ratio stratified by various factors influencing the endogenous production of PM2.5.

DISCUSSION

Air pollution has become a major concern in the past decade, with a raising number of acute air pollution occurrences in many cities worldwide. It accounted for 5.5 million premature deaths globally in 2013.[18] We have illustrated the ambient and indoor fine particulate matter in Bangkok Metropolitan Region, Thailand during February 20th to March 2nd, 2018. The median ambient PM2.5 mass concentrations during the study period (2018) was 29.18 μg/m^3, which was lower than reported annual median PM2.5 concentrations (55 μg/m^3) from South-East Asia in 2014. However, it is important to note that the trend of PM2.5 concentrations in South-East Asia during a five-year period (2008-2013) has been increasing more than 5% change.[1]

We measured the indoor PM2.5 concentrations in the closed ventilation settings to calculate I/A ratios because we hypothesized that this could reflect the real situation for indoor indwellers in Bangkok. Our data revealed that, the ambient PM2.5 concentrations dominate the indoor PM2.5 concentrations in most of the sampling sites. We found that there was a moderate to strong correlation between the ambient and indoor PM2.5 concentrations in all sites, reflecting the contribution of outdoor fine particulate matter to indoor air quality. Despite the closed ventilation system, the average I/A ratio from each place ranged from 0.37 to 3.57. It was clear that the outdoor PM2.5 can enter the buildings through three main ways, including natural ventilation, mechanical ventilation (air conditioning system), and infiltration. The I/A ratios could vary greatly because of the differences in indoor particle emission rates, the geometry of the cracks in building envelopes, and the air exchange rates. Penetration factor is an important factor for the penetration mechanism through cracks in the building envelope.[19]

According to the WHO Air Quality Guidelines (AQG) 2016, we compared the mean values of ambient and indoor PM2.5 mass concentrations with the AQG threshold level which was demonstrated in Fig 3. By using annual mean threshold (10 μg/m^3), all of the sampling sites (7 from 7 sites) exceeded the threshold level in both ambient and indoor PM2.5. When considering the short-term threshold (25 μg/m^3), the ambient PM2.5 concentrations of five from seven sites (71%) exceeded the threshold level and the indoor PM2.5 concentrations of three from seven sites (43%) exceeded the threshold level. The interventions to solve this problem should be launched and prioritized because a higher level of ambient PM2.5 concentrations are associated with the risk of various diseases, including cancers, cardiovascular diseases, and allergic diseases.

The prevalence of allergic airway diseases has increased significantly worldwide with the highest increase observed in industrialized nations.[20] The impact of particles on the human respiratory system is an issue of concern. In some countries, the morbidity for chronic respiratory diseases is much higher than other non-communicable diseases and the mortality from lung diseases is second to the accident.[21] Recent evidence has demonstrated the association between PM2.5 and asthma, respiratory inflammation, and impairment of lung functions. The pathomechanism of PM2.5 is determined by size, composition, origin, solubility, and ability for reactive oxygen species production.

We have demonstrated that indoor dwellers are still at risk to exposure to fine particulate matter, so this should be concerned. This emphasizes the need for indoor dwellers protection from PM2.5. Its impact on the human respiratory system should not be dismissed, especially the sensitive individuals such as asthmatic patients, children, and the elderly. Elderly individuals >65 years of age are more likely to spend a greater proportion of their time indoors and have multiple co-morbidities

which affect the overall morbidity. The environmental control strategies to reduce particle concentrations might improve the respiratory outcomes. The interventions reported to reduce the indoor PM2.5 concentrations included: reduction of the endogenous PM2.5 sources, sealing of cracks in the building envelope, a combination of the air conditioner, and air filter with efficient PM2.5 purification function.[16]

However, this study has some limitations. First, we did not measure some ambient air pollutants, such as O_3, NO_2, and SO_2 concentration data. As a result, our study could not extrapolate to the overall air pollution status. However, we measured PM2.5 which is the air pollutant that has been most closely studied and is most commonly used as a proxy indicator of exposure to air pollution more generally. Second, our study had the limited number of sampling sites and duration of data sampling. Therefore, our data may not be be reflective of the overall pollution situation in Thailand.

In conclusion, the indoor PM2.5 concentrations were correlated with the ambient PM2.5 concentrations. The concentrations of PM2.5 in most sampling sites were higher than the limited threshold. Hence, indoor dwellers are still at risk for health impacts from PM2.5. Besides public management of the ambient PM2.5, the interventions dealing with the indoor PM2.5 should be concurrently promoted.

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The Novel Assessment Tool for Scoring of Functional Outcomes after Surgical Release in Congenital Muscular Torticollis

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ABSTRACT

Objective: Congenital muscular torticollis, characterized by unilateral shortening of the sternocleidomastoid muscle that results in the head tilting towards the affected side, is the third most common musculoskeletal anomaly. Subjective assessment using the Lee scoring system has been the most common method for evaluating the surgical outcomes. The aim of this study was to investigate the efficacy of a novel assessment tool for scoring of functional outcomes after surgical release in congenital muscular torticollis.

Methods: This study enrolled the patients aged 5-15 years who were diagnosed with congenital muscular torticollis and treated by surgical release at the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 1998-2011. An image processing program was used to measure all evaluated parameters. Craniofacial asymmetry, neck rotation deficits, neck flexion/extension deficits, and degree of head-tilting were graded as poor, fair, good, or excellent by 2 observers. The results of the Lee scoring system and the new scoring system were then compared.

Results: Nineteen patients (7 males, 12 females) with a mean age of 7.2±2.57 years were included. Photographs of the patients were evaluated and categorized by outcome score using both outcome scoring systems. All intraclass correlation coefficients were higher than 0.6 for both scoring systems, which suggests good inter-operator reliability ($p<0.05$). Percentage agreement was higher in the new system than in the Lee system (63.16% *vs.* 52.63%, respectively).

Conclusion: The new outcome scoring system which focuses on functional outcomes after surgical release was found to be less subjective and more reliable than the Lee scoring system.

Keywords: Thailand; novel assessment tool; scoring; functional outcome; surgical release; congenital muscular torticollis (Siriraj Med J 2018;70: 272-277)

INTRODUCTION

The word *torticollis* is derived from two Latin words. The word *tortus* means crooked or twisted, and the word *collum* means neck.[1] Congenital muscular torticollis is the third most common musculoskeletal anomaly.[2] The overall incidence is this disorder ranges from 0.3% to 1.9%.[3] The shortening of the sternocleidomastoid muscle results in the head being tilted towards the affected side, while the face and chin are pulled or rotated to the opposite side.[4] Patients normally present with a palpable mass in the sternocleidomastoid muscle (SCM) on the affected side. Non-operative treatment is the gold standard treatment for patients less than 1 year of age, with treatment consisting of physical therapy and orthosis.

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Operative treatment is indicated in neglected cases, and in cases with residual deformity after physical therapy. The surgical techniques are bipolar or unipolar release and subperiosteal lengthening. The optimal surgical window is between 1 and 4 years of age. The surgical outcome is less predictable after 4 years of age, with permanent craniofacial deformity developing in some cases.[5]

The Lee scoring system[6] and the modified Lee scoring system[7] are both currently used to evaluate surgical outcome in congenital muscular torticollis. These systems are both based on subjective evaluation of functional and cosmetic outcomes. However and until now, no scoring system has been introduced that facilitates the objective evaluation of surgical outcome in patients with congenital muscular torticollis.

Accordingly, the aim of this study was to investigate the efficacy of a novel assessment tool for scoring functional outcome of surgical release in congenital muscular torticollis.

MATERIALS AND METHODS

This study enrolled and evaluated pediatric patients aged 5-15 years that were diagnosed with congenital muscular torticollis and treated by surgical release at the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the 1998 to 2011 study period. Siriraj Hospital is Thailand's largest national tertiary referral center. Patients who had undergone previous neck surgery, and those who were diagnosed with congenital muscular torticollis caused by other syndromes were excluded. This study was approved by the Siriraj Institutional Review Board (Si 049/2013).

Patient data were obtained either from direct contact with our patients at our outpatient follow-up clinic or via post/email. Patients that we could not communicate with person-to-person were asked to take photographs of themselves in 9 different views/positions, including (1) front view, (2) neck flexion, (3) neck extension, (4) head tilted left, (5) head tilted right, (6) head rotated to the left from anterior view and (7) lateral view, and (8) head rotated to the right from anterior view and (9) lateral view (Fig 1).

ImageJ® image processing program (National Institutes of Health, Bethesda, MD, USA) was used to measure each parameter

For neck flexion and extension angles, we measured from the lateral view. The angle between a vertical line perpendicular to the ground and a line drawn from the vertex of the head (longitudinal axis) to the middle part of the neck in the flexion and extension positions was evaluated (Fig 2). For head-tilt angle, we measured from the anteroposterior (AP) view with the head tilted left and right. The angle between a line drawn as a longitudinal axis of the face and a vertical line perpendicular to the ground was evaluated (Fig 3). For neck rotation, we measured from the AP view. The distance from the tip of the chin to the tip of the acromion on each side was evaluated (Fig 4). A full frontal facial view was used to evaluate the facial area. The area at the lower half of face between the lines drawn from the tip of the nose to the tip of the chin, and to the lateral edge of each side of the face was evaluated (Fig 5).

After all parameters were evaluated, we compared head-tilt, neck rotation, and facial area data between sides, and calculated the deformity as a percentage compared to the normal side. For neck flexion and extension angles,



Fig 1. Nine photos of each patient in the shown positions were evaluated (neck flexion angles, neck extension angles, head-tilt angles, neck rotation angles, and facial area)

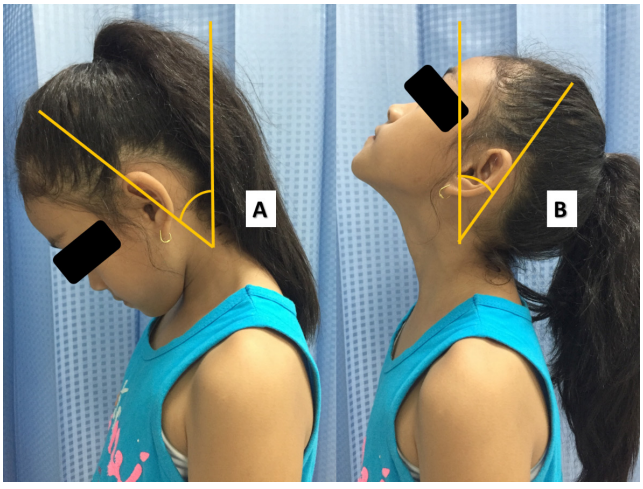


Fig 2. Measurement of neck flexion (A) and neck extension (B) angles



Fig 5. Measurement of facial area



Fig 3. Measurement of head-tilt angle



Fig 4. Measurement of neck rotation deficit distance for the normal (A) and affected (B) sides

we compared the measured value with the normal value, which is 60 degrees.

Scores ranged from 0 to 3 according to the percentage result compared to the normal side (Table 1). The sum of all individual parameter scores was then translated into 1 of the 4 following outcome classifications: poor, fair, good, or excellent (Table 2). All measurements were performed by 2 independent observers. The measurement data for each patient was then compared between the new scoring system and the Lee scoring system.

RESULTS

Nineteen pediatric patients were included. The mean age of patients was 7.2±2.57 years, and the gender proportion breakdown was 7 males and 12 females (Table 3). Nine photographs of each of the 19 included patients were evaluated and categorized by surgical outcome score using both surgical outcome scoring systems. The intraclass correlation coefficients for all measurements in both scoring systems were higher than 0.6, which suggests good interrater reliability ($p<0.05$). Percentage agreement in the new scoring system was 63.16% (95%CI of 38.63%-82.77%) and ICC is 0.867 (95%CI of 0.66-0.948) (Table 4), which is markedly higher than the percentage agreement of 52.63% in the Lee scoring system (Table 5).

DISCUSSION

The Lee scoring system[6] was the first generally accepted tool for assessing surgical outcome in congenital muscular torticollis; however, its scoring design is regarded as being excessively subjective. The modified Lee scoring system[7] that was later introduced included improvements over the original version, but the evaluation of surgical outcome

TABLE 1. Scoring matrix for the new scoring system based on percentage deficit compared to normal side ranges from 0 (0-25%), 1 (26-50%), 2 (51-75%) and 3 (76-100%) of each parameter

	76 – 100% (3)	51 – 75% (2)	26 – 50% (1)	0 – 25% (0)
Neck Flexion				
Neck Extension				
Head Tilt				
Neck Rotation				
Facial Asymmetry				

TABLE 2. Scoring and associated outcome classification of the new scoring system

Score	Outcome
13 – 15	Excellent
10 – 12	Good
7 – 9	Fair
≤ 6	Poor

TABLE 3. Demographic and clinical characteristics

Characteristics	(N=19)
Female gender, n (%)	12 (63.2%)
Age (yrs), mean±SD	7.2±2.57
Post-op duration (yrs), mean±SD	5.7±2.26
Affected side (left:right)	9:10

Abbreviation: SD, standard deviation

TABLE 4. New scoring system from 2 observers (N=19)

Patient no.	Observer 1 Total score	Outcome	Observer 2 Total score	Outcome
1	9	Poor	9	Poor
2	11	Fair	11	Fair
3	14	Excellent	12	Good
4	13	Good	13	Good
5	12	Good	15	Excellent
6	11	Fair	11	Fair
7	12	Good	12	Good
8	12	Good	11	Fair
9	12	Good	11	Fair
10	14	Excellent	15	Excellent
11	13	Good	11	Fair
12	10	Fair	10	Fair
13	11	Fair	11	Fair
14	10	Fair	10	Fair
15	13	Good	13	Good
16	11	Fair	11	Fair
17	11	Fair	12	Good
18	9	Poor	13	Good
19	12	Good	12	Good

is still largely subjective. Until now, no system has been introduced that facilitates more objective evaluation of surgical outcome in congenital muscular torticollis.

In this study, we set forth to develop a system that could yield a reliable and more objective for evaluating treatment outcome in this patient population. Our analysis revealed intraclass correlation coefficients for all measurements in both surgical outcome scoring systems to be above 0.6, which indicates good interrater reliability. However, percentage agreement in the new scoring system introduced here was considerably higher than in the Lee scoring system. The new scoring system evaluated in this study was shown to be more reliable for evaluating functional outcome of surgical release in congenital muscular torticollis.

CONCLUSION

The new outcome scoring system, which focuses on functional outcome of surgical release in congenital muscular torticollis, was found to be less subjective and more reliable than the Lee scoring system. Adoption and use of the new system introduced here may improve the accuracy of surgical outcome evaluation in patients with congenital muscular torticollis.

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TABLE 5. Lee scoring system from 2 observers (N=19)

Patient no.	Observer 1 Total score	Outcome	Observer 2 Total score	Outcome
1	9	Poor	8	Poor
2	10	Poor	10	Poor
3	14	Fair	14	Fair
4	15	Good	15	Good
5	15	Good	13	Fair
6	17	Excellent	15	Good
7	17	Excellent	15	Good
8	11	Poor	12	Poor
9	17	Excellent	13	Fair
10	17	Excellent	16	Good
11	14	Fair	14	Fair
12	12	Poor	13	Fair
13	11	Poor	9	Poor
14	15	Good	17	Excellent
15	16	Good	12	Poor
16	10	Poor	10	Poor
17	12	Poor	15	Good
18	12	Poor	11	Poor
19	17	Excellent	17	Excellent

Conflict of interest declaration: All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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A Comparison of Mechanical Thrombectomy for Large Vessel Occlusion in Acute Ischemic Stroke between Patients with and without Atrial Fibrillation

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ABSTRACT

Objective: Atrial fibrillation (AF) is one of the major risk for large vessel acute ischemic stroke. Mechanical thrombectomy is a promising therapeutic adjunct for large vessel occlusion and also the option for patients who missed the golden time window or who have contraindications for intravenous recombinant tissue plasminogen activator (rtPA). The purpose of this study was to investigate whether AF is a prognostic predictor for the patients with ischemic stroke undergoing mechanical thrombectomy.

Methods: Medical records of all patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO) who received mechanical thrombectomy at Siriraj Hospital between November 2009 and November 2016 were retrospectively reviewed. Clinical parameters between the two groups were retrieved and compared.

Results: One hundred and thirty -eight acute ischemic stroke (AIS) patients were treated by endovascular mechanical thrombectomy at Siriraj Hospital between November 2009 and November 2016. Five patients lost from the follow-up process. Totally, 134 patients were included to this study. Fifty patients (37.3%) were in the AF group, 10 patients (7.5%) had a newly diagnosed AF. The AF patients were younger (p=0.002) and had less intracranial atherosclerosis (p=0.015) than non-AF patients. Nevertheless, gender, mean NIHSS, the mean time form puncture to recanalization, mean onset to recanalization, number of the passing of the stent, TICI, symptomatic intracranial hemorrhage, good clinical outcome at 90 days, and mortality rate were not different between two groups.

Conclusion: There is no significant difference of good outcome and complications between AF and non-AF patients with AIS from LVO who underwent mechanical thrombectomy.

Keywords: Acute ischemic stroke; atrial fibrillation; mechanical thrombectomy (Siriraj Med J 2018;70: 278-283)

INTRODUCTION

In the setting of large vessel occlusion (LVO) with intravenous tissue plasminogen activator (IV-tPA), it is associated with low rate of recanalization and high rate of neurological morbidity and mortality. Mechanical thrombectomy is a promising therapeutic adjunct to IV-tPA for the treatment of acute LVO.

The results of the endovascular treatment for acute ischemic stroke were proved to reduce disability among patients with ischemic stroke treated with mechanical thrombectomy in addition to standard care.[1]

To date, at least five additional endovascular stroke randomized controlled trials; Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Extending the time for thrombolysis in

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emergency neurological deficits--intra-arterial (EXTEND-IA), Solitaire with the Intention for thrombectomy as primary endovascular treatment (SWIFT PRIME), Randomized trial of revascularization with solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight hours of symptom onset (REVASCAT) and Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke(THRACE) were halted prematurely for efficacy.[2-6] Many reports of mechanical thrombectomy showed a significant improvement in the rate of functional independence, with an absolute difference of 8-31 percent.[7]

Atrial fibrillation (AF) is globally considered one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity. Furthermore, the number of patients with AF was predicted to considerably rise in the coming years.[8] In 2010, the number of men and women with AF worldwide was estimated for 20.9 and 12.6 million people, respectively. Moreover, higher incidence and prevalence would be observed in developed countries.[9-10] By 2030, 14 – 17 million AF patients were anticipated in the European Union, with 120,000 – 215,000 newly diagnosed patients per year.[9,11-12]

AF prevalence is approximately 3% in adults aged 20 years or older,[13-14] with greater prevalence in older persons[9] and in patients with conditions, such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease.[15-20] Moreover, AF is considered an independent risk factor for stroke and increases its incidence nearly 5 folds.[21] The attributable risk of stroke for AF rises proportional to age, from 1.5% for those aged 50 to 59 years to 23.5% for those aged 80 to 89 years. Furthermore, AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men.[22-24]

In both developed and developing countries, the age-adjusted incidence and prevalence of AF are lower in women, while the risk of death in AF women is similar to or higher than that in AF men.[9,25] Besides, female AF patients who have additional stroke risk factors (particularly older age) also possess greater risk than men having a stroke, even those anticoagulated with warfarin.[26-28]

Randomized clinical trials in AF showed that an average annual stroke rate was about 1.5% and the annualized death rate was approximately 3% in anticoagulated AF patients.[29] The most important risk factors for stroke in patients with AF include advanced age and previous cardioembolic stroke or transient ischemic attack (TIA).[30] Moreover, AF is an important risk factor for ischemic stroke, which accounts for approximately 21-37% of the patients with ischemic stroke.[31]

The aim of this study was to investigate whether AF is a prognostic predictor for patients with ischemic stroke undergoing mechanical thrombectomy.

MATERIALS AND METHODS

Medical records of patients visiting Siriraj Hospital with ischemic stroke caused by LVO, together with salvageable tissues from CT perfusion or multiphase CTA and could come to follow up at the hospital by 90 days from November 2009 to November 2016 were retrospectively reviewed. Inclusion criteria were as followed: 1) those who had LVO in anterior circulation stroke within 8 hours with Alberta Stroke Program Early CT Score (ASPECTS) more than 6 points, or collateral score more than 3 points, or mismatched area more than 2/3 of the territory or 2) those who had LVO of posterior circulation stroke without clinical or imaging of brainstem infarction.

The patients, who were eligible, received intravenous-tPA immediately before CT angiography.[4,6-7] The effect of IV-tPA was not considered to be a criteria of patient selection for mechanical thrombectomy. (comment WU1) In addition, informed consent was signed by individual patients or their family members. However, exclusion criteria were as followed: 1) life expectancy was less than 3 months 2) platelets were less than 30,000/cubic millimeters (mm^3) 3) subarachnoid hemorrhage (SAH) or intracranial hemorrhage 4) massive brain edema from any causes 5) history of severe allergy to contrast media 6) clinical-radiographic match 7) extensive brainstem infarction.

Intracranial atherosclerosis was presumed if a residual stenosis of the affected vessel was presented, after recanalization. (comment WU2)

The diagnostic criteria for AF were as followed: P wave disappeared and was replaced by series of atrial fibrillation waves of various size, shape, and interval. Besides, atrial rate was 350-600 beats per minute and had completely irregular ventricular rate. In addition, QRS wave showed supraventricular form or widened deformity. Furthermore, AF was also established for those without f waves but with completely irregular RR intervals.

Statistical analysis; All data were manipulated and analyzed statistically with SPSS (version 21, SPSS Inc., Chicago, III., USA). The descriptive data were reported as mean with standard deviation or median with interquartile length and analyzed using unpaired t-test with unequal

variance or Mann-Whitney U test depending on the underlying data distribution. Categorical and dichotomized variables were described as a percentage and analyzed using Fisher's exact test. Unadjusted outcome effect sizes were estimated as differences in mean, median, or odds ratios (OR) with 95% CI as appropriate. P<0.05 was regarded as statistically significant.

RESULTS

One hundred and thirty eight patients with acute ischemic stroke (AIS) were treated by endovascular mechanical thrombectomy at Siriraj Hospital between November 2009 and November 2016. Of those, five patients did not visit the doctor for follow-up. Accordingly, 134 patients were included in this study, with the mean age of 64.2 years old. It consisted of 78 male and 56 female patients. Mean for the National Institutes of Health Stroke Scale (NIHSS) was 17.2. The anterior circulation stroke was found 80%. Intravenous rtPA had indication in 21.6% of patients. Intracranial atherosclerosis disease (ICAD) was documented in 18.7%

The mean time from puncture to recanalization was 94 minutes. The mean time from onset to recanalization was 401 minutes. Symptomatic hemorrhage was found 13.5%. The rate of good recanalization, determine by Thrombolysis in cerebral infarction (TICI) 2B and 3, was 76.1%. The good outcome (modified Rankin scale ≤ 2) at 90 days was found 38.3%. In addition, baseline data, results, and complications between AF and non-AF groups are shown in Table 1.

According to Table 1, age of patients in AF group was significantly older than those in non-AF group (p=0.002). In addition, intracranial atherosclerosis disease in AF patients was significantly less than that in AF patients (p=0.015). Nevertheless, sex, mean NIHSS, mean time from puncture to recanalization, mean time from onset to recanalization, the number of pass of the stent, TICI, symptomatic intracranial hemorrhage, good clinical outcome at 90 days, and mortality rate were not significantly different between two groups.

In the present study, 10 patients had a newly diagnosed AF (AF was diagnosed at onset of stroke or within 1 week

TABLE 1. Parameters between AF and non-AF patients.

Parameters	Total (N=134)	AF group (N=50)	Non-AF group (N=84)	P value
Age	63.9 ± 15.5	69.2 ±12.9	60.2 ±16.0	0.002*
Male sex (n. %)	78 (57.9%)	27 (54%)	51 (60.7%)	0.446
NIHSS score (118 cases)	17.2 ± 6.0	17.4 ± 5.5	17.1 ± 6.3	0.769
IV-tPA (n. %)	29 (21.6%)	10 (20%)	19 (22.6%)	0.722
ICAD (n. %)	25 (18.7%)	4 (8%)	21 (25%)	0.015*
mRS ≤ 2 at 90 day	51 (38.1%)	19 (38%)	32 (38.1%)	0.570
Puncture to recanalization time (min)	93.8 ±103.7	109.3	84.5	0.181
Onset-to-recanalization time (min)	400.3 ± 264.6	358.0	425.4	0.155
Number of pass of stent median ($p25^{th}$- $p75^{th}$)	2.75	3 (2-4)	2 (1-3.75)	0.103
Symptomatic ICH (n. %)	17 (12.7%)	6 (12%)	11 (13.1%)	0.854
TICI2b,3	102 (76.1%)	38(76%)	64(76.2%)	0.948
mortality rate	26 (19.4%)	10(20%)	16(19%)	0.893
Anterior circulation	107 (80%)	43 (86%)	64(76.2%)	0.355
Posterior circulation	27 (20%)	7(14%)	20(23.8%)	

*Values with P < 0.05 are considered statistical significant

during being admitted in hospital) and 40 patients were documented AF, One patient had intracardiac clot and poor outcome after treatment.

In the AF group, the good outcome was found 42.8% (18/42) in patients with good controlled AF, whereas 12.5% (1/8) in patients with uncontrolled AF (p 0.134).

Results of mechanical thrombectomy between patients with anterior and posterior circulation stroke showed no different outcome (p 0.847) in the present study.

DISCUSSION

Presently, in Thailand, the number of people aged 60 years old and over stands at 8 million heads (13% of total population). By 2040, Thailand aging population is expected to 17 million heads (25%of total population); prevalence of AF in Thai population was expected to 3.46%.[32]

AF is an important risk factor for ischemic stroke. AF-induced ischemic stroke presented more severe symptoms and poorer prognosis.[33] An AF-induced thrombus was often larger than one resulting from atherosclerosis and had a higher proportion of older thrombus.[34] AF was associated with greater volumes of more severe baseline hypoperfusion, leading to higher infarct growth, more frequent severe hemorrhagic transformation, and worse stroke outcomes.[35]

It has been postulated that patients with AF had less developed cerebral collateral circulation because the majority did not have concomitant carotid or intracranial large artery stenosis.[36] Stroke due to intracranial large artery stenosis have previously been shown to have better collateral circulation than that due to extracranial large artery stenosis, cardio-embolism, and undetermined causes.[37,38]

In the limited relevant studies, higher probability of poor prognosis and bleeding was found in ischemic stroke patients with AF after intravenous thrombolytic therapy than in those without AF.[39-40] However, an evidence from the Virtual International Stroke Trials Archive (VISTA) showed that the presence of atrial fibrillation had no independent impact on stroke outcome at 90 days. Among patients with atrial fibrillation, baseline severity (median NIHSS) was greater (p=0.001) and age was higher (p=0.001).

From IV-tPA data, the patients who received thrombolysis experienced an advantage in outcomes that were of equal magnitude whether, in the presence or absence of atrial fibrillation, rate of ICH were similar in both AF and non-AF groups.

According to endovascular aspect, data from China were limited as 35 cases enrolled. Of those, they were 10 cases for AF and 25 cases for non-AF groups. That study found similar percentage of good outcome in both groups after treatment. Nonetheless, patients in AF group had higher percentage of recanalization rate than those in non-AF group.[41] (Table 2)

TABLE 2. Factors relevant to good outcome for mechanical thrombectomy.

Parameters		Poor outcome (mRS >2)	Good outcome (mRS < 2)	P value
Age		66.83±14.1	59.10±16.5	0.005*
Mean NIHSS		18.5	15.6	0.010*
IV-tPA		15 (51.7)	14 (48.3)	0.087
ICAD		18 (16.5%)	7 (28%)	0.254
TICI 2b,3		56 (54.9)	46 (45.1)	0.268
Puncture-to-recanalization time (min)		80	64	0.020*
Onset-to-recanalization time (min)		344	315	0.063
Sex	Male (n. %)	51	27	0.105
	Female (n. %)	24	32	
Site	Anterior (n. %)	66 (61.7%)	41 (38.3%)	0.847
	Posterior (n. %)	17 (63%)	10 (37%)	

*Values with P < 0.05 are considered statistical significant

In the current study, it was composed of 50 cases in AF group and 84 cases in non-AF group. We found that good outcome was not significantly different between AF and non-AF groups (38% vs 38.1%, p=0.991). However, mean age of patient in AF group was higher than those in non-AF group (69.24 vs 60.70 years, p.002). As for sex, NIHSS, receiving IV r-TPA before treatment, site of occlusion, intracranial stenosis, time of operation, number of pass of stent, symptomatic hemorrhage, and good controlled AF, they were not statistically significant between two groups. It meant that AF in AIS patients undergoing mechanical thrombectomy was not associated with a poor outcome.

For posterior circulation stroke, selected patients who remained brain stem tissue and received mechanical thrombectomy had a same good result rate as patients with anterior circulation stroke. This is the surprising data because most data indicated that posterior circulation stroke was associated with very poor outcome. Young age, low NIHSS, and short procedural time were associated with good outcome at 90 days.

CONCLUSION

We supported that endovascular mechanical thrombectomy was beneficial to LVO patients in both AF and non-AF with AIS. Moreover, this approach demonstrated no difference of complications and mortality rate between both groups. The AF patients with AIS was not associated with a poor outcome with mechanical thrombectomy.

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The Normal Reference Values of Carrying Angle from Birth to Adolescence

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ABSTRACT

Objective: The aim of this study was to establish normal carrying angle reference values from birth to adolescence, and to identify variations in carrying angle relative to age, gender, and elbow side.

Methods: The prospective cross-sectional study was performed in normal healthy children aged newborn to sixteen years during May 1959 to April 1961. Children were recruited from newborn units, nurseries, and schools located in Bangkok, Thailand. There was a total of 17 groups – one for each year of age from 0 (at birth) to 16. The carrying angles of both arms were measured using a clear plastic full-circle orthopedic goniometer. The data of age, side, and gender of each child were recorded.

Results: A total of 921 children with 1,842 measurements were included. There were 407 boys and 514 girls. The mean carrying angle was lowest at birth and highest in the 15- year and 16-year age groups. The increase in the carrying angle was observed to progress to valgus 6 degrees at 6 years of age, and to valgus 11 degrees and stabilization at 15 years of age. There was no statistically significant difference between the mean carrying angle of the left and right side for any of the 17 evaluated age groups. Girls demonstrated a significantly greater carrying angle than boys ($p<0.001$). The intraclass correlation coefficient (ICC) of inter-observer variation between two observers was 0.848.

Conclusion: This study established normal carrying angle reference values from birth to adolescence. Our results revealed that the elbow is slightly varus at birth, then increases in carrying angle until reaching stabilization of skeletal growth and development at 15 years of age. The carrying angle is slightly greater in girls than in boys. This normal reference value data will benefit orthopedists who take care of the pediatric patients with elbow-related disorders.

Keywords: Reference value; carrying angle; birth; adolescence; elbow (Siriraj Med J 2018;70: 284-288)

INTRODUCTION

The carrying angle is clinically defined as the angle made by the longitudinal axis of the arm and the forearm in full extension with the elbow supinated. In children, the carrying angle is an important outcome measure that is routinely used during treatment of fractures around the elbow. Increased carrying angle is referred to as cubitus valgus, and decreased carrying angle is termed cubitus varus. Cubitus varus deformity is one of the common complications of supracondylar humeral fracture, lateral condyle fracture, and transphyseal fracture in children. For the body to appear cosmetically normal, the carrying angle of both elbows should be equal or nearly equal.[1] Normal carrying angle reference values can help us determine the cosmetically-acceptable limits of deformity in specific age groups.

Of the studies that have reported on normal carrying angle reference values, few have focused on

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children.[2] One study from Northern Thailand measured carrying angle in adults aged 18-35 years.[2] It is often reported that the carrying angle increases with age, and is greater in girls than boys[2,3,4]; however, conflicting data has been reported.[5] In studies that have reported on carrying angle in children, most focused a specific age range (e.g., 3-19 years of age), but none studied children from birth to adolescence.[2-13]

To our knowledge and based on our review of the literature, no previous reports have been published that describe normal carrying angle reference values throughout childhood in pediatric population. Accordingly, the aim of this study was to establish normal carrying angle reference values from birth to adolescence, and to identify variations in carrying angle relative to age, gender, and elbow side.

MATERIALS AND METHODS

The prospective cross-sectional study was performed in normal healthy children aged newborn to sixteen years at the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University during the May 1959 to April 1961 study period. Children with any history of elbow trauma, deformity, or disease that affects the elbow, such as skeletal dysplasia and rickets, were excluded. Children from newborn units, nurseries, and schools located in Bangkok, Thailand were included. There were a total of 17 groups – one for each year of age from 0 (at birth) to 16. The study and all of the measurement methods and protocols were approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 684/2013).

The carrying angle was measured using a clear plastic full-circle orthopedic goniometer (Fig 1) according to the method previously described by Amis and Miller.[8] This method was used in several other studies[9,10,11], and was reported to be accurate, with an error margin of ≤1 degree.[9] The arm was abducted to 90 degrees over a straight table, with the forearm in full extension and supination. The hinge of the goniometer was positioned at the center of the cubital crease, and the arms of the goniometer arms were positioned parallel to the middle longitudinal axes of the arm and forearm. A minus sign (-) indicates varus angle, and a plus sign (+) indicates valgus angle. Both arms were measured, and the age, side, and gender of each child were recorded.

Statistical analysis

All data analyses were performed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Mean normal carrying angle reference values were calculated and statistically compared between and among age groups to identify differences relative to age, gender and elbow side. Data are presented as number, percentage, or mean ± standard deviation. Intraclass correlation coefficients were calculated and analyzed to measure interrater agreement. A *p*-value less than 0.05 was regarded as being statistically significant.



Fig 1. The carrying angle was measured using a clear plastic full-circle orthopedic goniometer. The upper extremity was abducted to 90 degrees over a straight table, with the forearm in full extension and supination. The hinge of the goniometer was positioned at the center of the cubital crease, and the arms of the goniometer arms were positioned parallel to the middle longitudinal axes of the arm and forearm. Both arms were measured. A minus sign (-) indicates varus angle, and a plus sign (+) indicates valgus angle. The carrying angle measured in this right elbow was +23 degree.

RESULTS

The 921 children that were included had both elbows measured for a total of 1,842 sides. There were 407 boys and 514 girls that were divided into 17 groups by year from 0 (at birth) to 16 years.

The mean normal carrying angle reference values for each age group by elbow side from birth to age 16 years are shown in Table 1. The mean carrying angle was lowest at birth (mean varus: 1.49 degrees) and highest in the 15- and 16-year age groups (mean valgus: 11

TABLE 1. Mean normal carrying angle reference values for each age group by elbow side from birth to age 16 years

Age (yrs)	Arm side	Number of sides	Mean carrying angle (degrees)	SD	*P*-value*
0 (at birth)	Right	74	-1.3	1.7	0.06
	Left	74	-1.6	1.7	
	Both	148	-1.5	1.7	
1	Right	15	+4	2.8	0.8
	Left	15	+3.8	2.4	
	Both	30	+3.9	2.5	
2	Right	34	+5.9	2.6	0.5
	Left	34	+5.7	2.4	
	Both	68	+5.8	2.4	
3	Right	26	+6.9	2.5	0.6
	Left	26	+6.7	2.8	
	Both	52	+6.8	2.6	
4	Right	31	+6	2.2	0.9
	Left	31	+6	2.6	
	Both	62	+6	2.4	
5	Right	39	+6.1	3.2	0.9
	Left	39	+5.9	3.2	
	Both	78	+6	3.2	
6	Right	26	+5.9	2.1	0.4
	Left	26	+6	2.6	
	Both	52	+6	2.4	
7	Right	22	+7.6	3.3	0.6
	Left	22	+7.3	3.5	
	Both	44	+7.4	3.4	
8	Right	79	+8.2	2.3	0.9
	Left	79	+8.2	2.3	
	Both	158	+8.2	2.3	
9	Right	143	+8.6	2.7	0.06
	Left	143	+8.3	2.8	
	Both	286	+8.4	2.7	
10	Right	126	+8.9	2.6	0.3
	Left	126	+9.1	2.7	
	Both	252	+9	2.7	
11	Right	79	+9.6	2.7	0.3
	Left	79	+9.4	2.7	
	Both	158	+9.5	2.7	
12	Right	54	+10.3	2.8	0.8
	Left	54	+10.2	2.7	
	Both	108	+10.3	2.7	
13	Right	77	+9.7	2.2	0.4
	Left	77	+9.7	2.1	
	Both	154	+9.7	2.1	
14	Right	40	+10.5	2.6	0.4
	Left	40	+10.6	2.5	
	Both	80	+10.6	2.5	
15	Right	37	+11.1	3.2	0.6
	Left	37	+11	3.4	
	Both	74	+11	3.2	
16	Right	19	+11.1	2.5	0.2
	Left	19	+11.5	2.9	
	Both	38	+11.3	2.7	

A *p*-value<0.05 indicates statistical significance

*The *p*-value is the statistical difference compared the mean carrying angle of right and left side in the same group.

Abbreviations: SD, standard deviation; '-', the angle is in varus of the elbow; '+' the angle is in valgus of the elbow

degrees). Increase in the carrying angle was observed to progress to valgus 6 degrees at 6 years of age, and to valgus 11 degrees and stabilization at ≥15 years of age. There was no statistically significant difference between the mean carrying angle of the left and right side for any of the 17 evaluated age groups ($p>0.05$).

The mean carrying angle among all age groups, with the angle values of the left and right side added together, was valgus 7.8±4.1 degrees. In comparison of mean carrying angle between age group, the statistically significant difference was obtained between age group ($p<0.001$).

The mean carrying angle was valgus 6.9±3.8 degrees in boys, and valgus 8.5±4.1 degrees in girls. Girls demonstrated a significantly greater carrying angle than boys ($p<0.001$) (Table 2).

A graph describing the mean (±2 standard deviations) normal carrying angle reference value for each age group is shown in Fig 2.

The intraclass correlation coefficient (ICC) of interobserver variation between two observers in 537 cases was 0.848 (95% confidence interval: 0.818-0.872), which indicated minimal variation between observers.

TABLE 2. Comparison of carrying angle between boys and girls (N=921)

Gender	Number of children	Number of sides	Percent	Mean carrying angle	SD	*P*-value
Boys	407	814	55.8%	+6.9	3.8	<0.001
Girls	514	1,028	44.2%	+8.5	4.1	

A p-value<0.05 indicates statistical significance
Abbreviation: SD, standard deviation

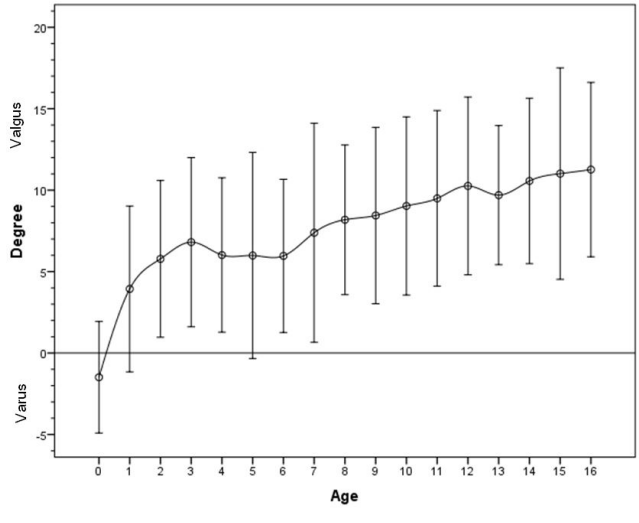


Fig 2. Normal carrying angle reference values (mean ± 2 standard deviations) from birth to 16 years. Degree values less than and greater than zero indicate varus of the elbow and valgus of the elbow, respectively.

DISCUSSION

This study provides new knowledge about normal carrying angle values from birth to adolescence, and about the development and progression of angle from slightly varus at birth to valgus and stable at 15-16 years of age (Table 1, Fig 2). The next study in carrying angle should focus on age group given the differences among age groups, especially in young children and adolescents. The present study and other studies found and reported age-dependent changes in the carrying angle.[3,6,7] The findings of this study confirm the reported findings of other studies that the carrying angle increases with age as a result of skeletal growth and development.[9,10,12]

With the exception of the study by Beals[5] who reported equality of carrying angle between genders, the present study and many others found a slightly greater carrying angle in girls than in boys.[2-4,6,7,10-13] The difference in findings between Beals' study and others may be due to differences in angle measurement method (measurement from radiographic imaging vs. measurement by goniometer), race of the study population, and sample size.

Some studies reported a greater carrying angle on the dominant side.[7,10] Since dominant side is not yet determined in very young children, and it could be

difficult to elicit from other age groups, we decided not to include this factor in our analysis.

The pediatric carrying angle data yielded by this study can be used as a comparative benchmark against clinical measurement in routine practice, or against radiographic measurement of the elbow.

CONCLUSION

This study established normal carrying angle reference values from birth to adolescence. Our results revealed that the elbow is slightly varus at birth, with increases in carrying angle until stabilization of skeletal growth and development at 15 years of age. The carrying angle is slightly greater in girls than in boys. This normal reference value data will benefit orthopedists that treat and follow pediatric patients with elbow-related disorders.

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Cranial Dural Arteriovenous Fistulas: Can Non-invasive Imaging Predict Angiographic Findings?

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ABSTRACT

Objective: To access the practical of non-invasive diagnostic tools including computed tomography (CT) and magnetic resonance imaging (MRI) to determining the characteristics and aggressiveness of a cranial dural arteriovenous fistula (DAVF).

Methods: Retrospective review of patients with cranial DAVFs who had registered at the Interventional Neuroradiology Center, Siriraj Hospital between January 2007 and December 2016 was performed. The pre-treatment imaging findings were recorded for presence of diagnostic criteria of DAVF, number and location of shunts, and aggressiveness of the disease. Cerebral angiography was used as standard reference in each patient.

Results: There were 86 patients with 119 DAVFs, of which 70.6% were aggressive type. By non-invasive imaging criteria, the shunt detection rate was 95.3%. Inaccuracy of localization and aggressiveness pattern of the disease occurred in 10.4% and 5.9% of the cases respectively. Dural sinus thrombosis was shown in 38%. MRI was superior to CT in accuracy of multiplicity (76.7% VS 55.3%) and identification of aggressiveness (90.2% VS 80%).

Conclusion: Both CT scan and conventional MRI have capability in detection of DAVFs and identification of the disease aggressiveness. Diagnostic limitation and mistaken aggressiveness can occur in patients who have DAVFs with dural sinus drainage only. CT or MRI should be used in practice as the initial work up, with clinical correlation, to identify patients with DAVFs who require endovascular treatment at the appropriate time.

Keywords: Cranial dural arteriovenous fistulas; cerebral angiography; retrograded sinus drainage; cortical venous drainage (Siriraj Med J 2018;70: 289-297)

INTRODUCTION

Dural arteriovenous fistula (DAVF) is defined as an abnormal fistulous communication between the dural arteries and cerebral venous sinus and/or cortical veins.[1,2] A recent population-based study mentions its detection rate as 0.16 per 100,000 adults per year and is estimated to relate to approximately 10-15% of all intracranial arteriovenous malformations.[3-5]

Most DAVFs in adulthood are considered as an acquired lesion.[1,6] The exact etiology and pathogenesis of the DAVFs has remained controversial. Nevertheless, most of these lesions are thought to be secondary from dural venous sinus thrombosis.Venous occlusion results in venous congestion and increased venous pressure. Venous hypertension may increase angiogenic activity which lead to development of DAVFs.[6]

The symptoms of DAVFs depended on their locations and the venous drainage pattern, which ranges from asymptomatic, non-specific headache, focal cranial nerve deficit, exophthalmos, chemosis, pulsatile tinnitus, to

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even more aggressive symptoms such as motor and/or sensory deficits, seizure, dementia or even intracranial hemorrhage.[7,8]

Nowadays, various classifications are proposed which have mostly focused on the pattern of venous drainage, which is crucial in the risk assessment of these lesions. DAVFs with the presence of cortical venous drainage (CVD) or retrograded sinus drainage (RSD) or both are considered to have a higher risk of neurological sequelae and intracranial hemorrhage. For clinical and therapeutic consideration, DAVFs are classified into 2 major groups: benign and aggressive, by the absence and presence of CVD or RSD on angiographic study, respectively.[7,9]

Identification of DAVFs is crucial because it is a curable disease. The suspicion of the disease is leadby clinical presentation and imaging finding. Although the catheter-based cerebral angiography is currently regarded as the gold standard for diagnosis, and classification of the aggressiveness[10], the procedure is invasive and should be reserved for patients who require endovascular treatment.

Practically, patients who have clinical symptoms are usually first referred for non-invasive diagnostic imaging such as computed tomography (CT) and/ or magnetic resonance imaging (MRI), which are feasible tools in general practice. Hence, if they have diagnostic capability and accurate depiction for severity of DAVFs, this would be useful to rule-in patients who need to perform cerebral angiography and subsequent endovascular treatment, particularly if aggressive features present which require urgent specific care.

This study aimed to assess the practical applicability of non-invasive diagnostic imaging include CT and/ or MRI of the brain to determine characteristics and aggressiveness of DAVFs.

MATERIALS AND METHODS

This study was approved by the Human Research Committee, Siriraj Hospital (Si 692/2016). The records of 96 patients with DAVFs who had referred to Interventional Neuroradiology Center, Siriraj Hospital between January 2007 and December 2016 were retrospectively reviewed. The patients who had no pre-treatment diagnostic imaging (cranial CT and/or MRI) available in Siriraj picture archiving and communication system (PACS) or who had diagnostic study prior to catheter angiogram more than 6 months were excluded.

The pre-treatment imaging including cranial CT which were both noncontrast CT (NCCT) and contrast enhanced CT (CECT) and conventional MRI (with or without MR angiography) were reviewed by two authors who were one interventional neuroradiologist and one 2nd year interventional neuroradiologist fellow. They were blinded to patient's history, clinical presentation and results of cerebral angiographic examination. The discrepancies were resolved by discussion. The data collection included presence of diagnostic criteria of DAVFs, number and location of shunts, and aggressiveness of diseases. The presence of associated venous sinus thrombosis was also recorded. Imaging of the patients who had both CT and MRI examinations were reviewed in random sequence with the other patients.

The criteria for presence of DAVFs on both CT scan and MRI were demonstrable enlarged and/or early filling of dural sinus or venous structure(s) with or without detectable asymmetrically dilatation of external carotid arterial branch(es) that were located near the presumed fistulous point(s). (Fig 1)

The locations of DAVFs were presumed at the segmental enlargement of the dural sinus(es), which were identified as: jugular bulb, transverses-sigmoid sinus, cavernous sinus, superior sagittal sinus, torcular Herophili and straight sinus/ vein of Galen. The sites at transverse-sigmoid and cavernous sinuses were also recorded as left, right or bilateral.

The criteria for presence of CVD and/ or RSD were (Figs 2 and 3)

1. Early filling of the cortical veins
2. Asymmetrically rapid filling of dural sinus(es) that was proximal to the suspected DAVF location
3. Increase in the size and/or number of cortical veins

The DAVFs would be defined as aggressive if CVD and/ or RSD were present, and benign if CVD and RSD were absent.

In the specific location of DAVF at cavernous sinus, if only drainage through the superior ophthalmic vein (SOV) was demonstrated, it was considered as benign type.

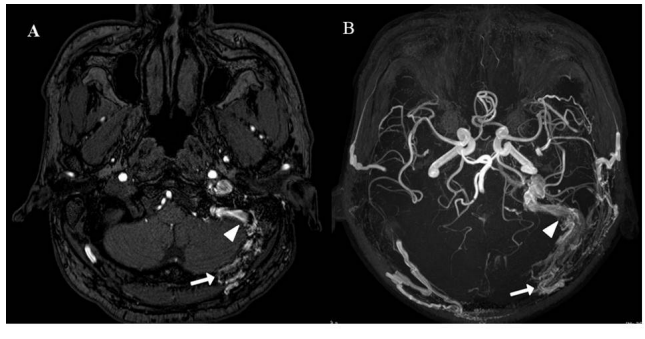


Fig 1. Criteria for presence of cranial dural arteriovenous fistula (DAVF). **(A)** MR angiography and **(B)** Maximum intensity projection (MIP) demonstrated dilated transosseous branches of left occipital artery (arrows) to supply the DAVF at left sigmoid sinus (arrowheads)

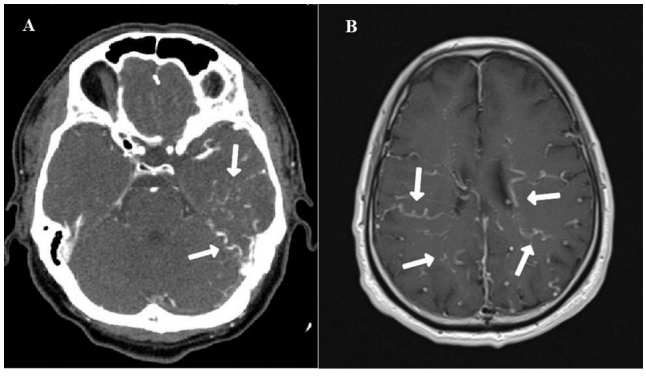


Fig 2. Criteria for presence of cortical venous drainage (CVD). **(A)** Contrast enhanced Computed Tomography (CECT) and **(B)** Post gadolinium T1W magnetic resonance imaging (MRI) in different patients showed dilatation and tortuosity of cortical veins (arrows).

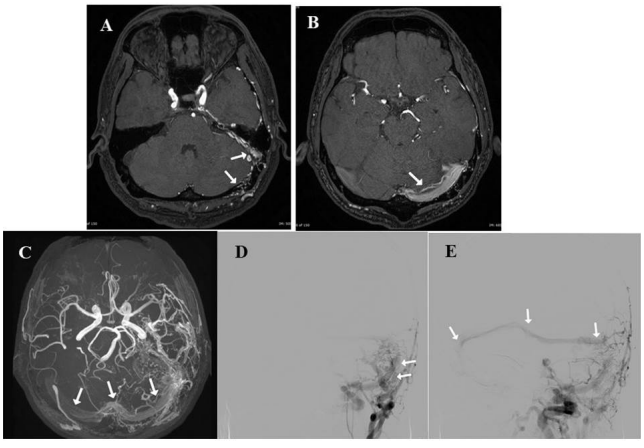


Fig 3. Left sigmoid cranial dural arteriovenous fistula (DAVF), aggressive type in a 49-year-old man who presented with pulsatile tinnitus.
(A)(B) MR angiography and **(C)** Maximum intensity projection (MIP) craniocaudal direction demonstrated cranial dural arteriovenous fistula (DAVF) at left sigmoid sinus (arrows in A) with visualized retrograded flow in bilateral transverse sinuses which were indicative of retrograded sinus drainage (RSD). No cortical venous drainage (CVD) was recognized.
(D) Early and **(E)** late arterial phases of left occipital angiography, frontal projection, revealed corresponding findings of cranial dural arteriovenous fistula (DAVF) at left sigmoid sinus with retrograded sinus reflux only. Also noted antegraded drainage of distal sigmoid sinus (arrows in D) without evidence of sinus thrombosis.

The CVD was recorded as "present" if there was early filling and/ or prominent size of the ipsilateral sphenoparietal sinus.

Catheter angiography was the gold standard for diagnosis of cranial DAVFs, shunt locations, characteristics of venous drainage pattern and type of fistula.

Data were prepared and analyzed using PASW statistics 18.0 (SPSS). Continuous data were described as mean and standard deviation (SD) or median and range, as appropriate. Numbers and percentages were expressed for categorical data and compared using Chi-square test or Fisher's exact test. All tests of significance were two tailed, and p-value of <0.05 was considered as statistical significant.

RESULTS

There were 86 patients with 119 DAVFs who were included in this study (50 women and 36 men with age range between 18-87 years and mean age at 56.17 ±14.25 years), 35 DAVFs (29.4%) were benign type and 84 (70.6%) were aggressive. Most patients (72.1%) had solitary DAVF, whereas 2 patients (2.3%) had maximal number of 4 fistulas.

The duration of clinical presentations varied from a few days to 24 months with mean duration at 2.4 months. The critical clinical presentations, including progressive neurological deficits, seizure, dementia and alteration of consciousness was correlated with aggressive type of DAVFS 96.2% (25/29 patients). Nevertheless, 54.4% (31/57) of patients who had non-serious clinical presentations, which were tinnitus, chemosis and headache, also had aggressive pattern. The angiographic characteristics of DAVFs were shown in the Table 1.

The common locations were cavernous sinuses (40.4%) and transverse-sigmoid sinuses (36.1%), respectively. Most benign DAVFs (54.3%) were found to be located at cavernous sinuses. The aggressive DAVFs were equally at transverse-sigmoid sinuses (35.7%) and cavernous sinuses (34.5%). All DAVFs demonstrated at superior sagittal sinus, torcular herophili and straight sinus had characteristics of aggressive pattern.

CT scans were performed in 43 cases (50%) with accompanying CT angiography in 37 (43%). MRI and MR angiography were available in 34 patients (40.5%), and only conventional MRI in 5 (5.8%). Both CT scan and MRI were carried out in 4 cases (4.7%).

The capability of diagnosis and characteristic identification of DAVFs from noninvasive imaging studies were demonstrated in Table 2.

The criteria of diagnosis of DAVFs were not recognised in 4 patients (4.7%), 3 from CT scan (1 CECT, 2 CT angiography) and the other one from the studies of MRI and MR angiography. Three of them were interpreted to be normal and one had reported to have dural sinus thrombosis only. Two patients had aggressive type showing RSD, without CVD. One patient with cavernous sinus location had antegraded drainage to inferior petrosal sinus only, without dilatation of superior ophthalmic vein.

TABLE 1. Angioarchitectures of cranial dural arteriovenous fistulas (DAVFs).

Characteristics	N (%)	Total N (%)
Aggressiveness		
Benign	35 (29.4%)	119 fistulas (100%)
Aggressive	84 (70.6%)	
Multiplicity		
One	62 (72.1%)	
Two	20 (23.3%)	86 patients (100%)
Three	2 (2.3%)	
Four	2 (2.3%)	
Location		
Cavernous sinus	48 (40.4%)	
Transverse-sigmoid sinus	43 (36.1%)	
Superior sagittal sinus	8 (6.7%)	119 fistulas (100%)
Jugular bulb	5 (4.2%)	
Torcular Herophili	13 (10.9%)	
Straight sinus/vein of Galen	2 (1.7%)	

TABLE 2. Diagnosis of cranial dural arteriovenous fistulas (DAVFs) from Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI).

Parameters	N (% Correction)	Total (N)
Identification of cranial dural arteriovenous fistulas (DAVFs)		
No	4 (4.7%)	86 patients
Yes	82 (95.3%)	
Location		
Undetermined location	9 (10.4%)	86 patients
Cavernous sinus	40 (83.3%)	48 fistulas
Right	19 (79.2%)	24 fistulas
Left	21 (87.5%)	24 fistulas
Transverse-sigmoid sinus	27 (62.8%)	43 fistulas
Right	8 (57.1%)	14 fistulas
Left	19 (65.5%)	29 fistulas
Superior sagittal sinus	2 (25.0%)	8 fistulas
Jugular bulb	4 (80.0%)	5 fistulas
Torcular Herophili	1 (7.7%)	13 fistulas
Straight sinus/ vein of Galen	1 (50.0%)	2 fistulas
Multiplicity		
One	47 (75.8%)	62 patients
Two	12 (60.0%)	20 patients
Venous sinus thrombosis		
Absent	56 (86.2%)	65 patients
Present	8 (38.1%)	21 patients
Aggressiveness		
Benign	27 (90.0%)	30 patients
Aggressive	46 (82.1%)	56 patients

DAVFs were able to diagnose, but failed to demonstrate their locations in 9 patients (10.4%). The cavernous sinus was the location of the highest percentage of correct detection (40 of 48 shunts, 83.3%), whereas the torcular herophilli was the lowest (1 of 13 shunts, 7.7%). Dural venous sinus thrombosis was recognized in only 38% (8/21 patients).

The multiplicity of DAVFs revealed by noninvasive studies were as many as two locations. MRI demonstrated more superior accuracy in detection of multiple DAVFs than CT studies, with the accuracy of 76.7% and 55.3%, respectively.

Concerning determination of DAVFs aggressiveness from CT studies, the percentage of correction was 80% (36/45), the sensitivity and specificity were 80.0% (95% CI: 61.4-92.3) and 80.0% (95%CI:51.9-95.7), respectively. Positive predictive value (PPV) was 88.9% (95%CI: 74.1-95.7) and negative predictive value (NPV) was 66.7% (95%CI: 48.3-81.0). From MRI studies, the correction was 90.2% (37/41), sensitivity and specificity were 78.9 % (95% CI: 54.4-94.0) and 95.6% (95%CI: 78.0-99.9), respectively. Positive predictive value (PPV) was 93.8% (95%CI: 68.5-99.0) and negative predictive value (NPV) was 84.6% (95%CI: 69.6-93.0). (Table 3)

There were 7 aggressive DAVFs (5.9%) which were interpreted as benign lesions, 4 by CT and 3 by MRI. Four cases had DAVFs at cavernous sinuses which demonstrated retrograded venous reflux into the sylvian veins on catheter angiography and the other three patients had lesions located at transverse-sigmoid sinuses with retrograded drainage to the other side of transverse sinuses, without evidence of CVD. The patient characteristics were shown in Table 4.

DISCUSSION

The common presenting symptoms of DAVFs in this study were pulsatile tinnitus and ocular symptoms, this was similar to previous reports in the literature.[4,11-12] Among these patients, about half of them were definitely aggressive type of DAVFs. Thus, the initial radiologic work-up would be crucial for assessment of brain parenchyma and for treatment planning. The usefulness of CT scan and MRI was proved for differentiation of vascular etiologies[13] Particularly in the suspicious case, for the negative imaging result it is impossible to exclude DAVF unless confirmed by cerebral angiography.

There were many reports of diagnostic clues of DAVFs on non-invasive imaging studies, such as the visualization of asymmetrical enlargement of arterial feeders, shaggy appearance of the dural sinus, asymmetrical dural sinus enhancement, trans-calvarial vascular channels, trans-osseous vessel enhancement, and asymmetrical attenuation of jugular veins on CT angiography.[14-16] The presence of flow void along the dural sinus margin in conventional MRI and flow-related enhancement around the dural sinus or cerebral vein were the suggestive evidences on MR angiography.[17-20]

The criteria for diagnosis of DAVFs which were used in this study could provide 95.3% of shunt detection rates.

TABLE 3. Comparison of cranial dural arteriovenous fistula (DAVF) classification for aggressiveness between noninvasive images and angiography.

Noninvasive classification		Angiographic classification		
		Benign	Aggressive	Total
CT	Unclassified	1	2	3
	Benign	12	4	16
	Aggressive	2	24	26
	Total	15	30	45
MR	Unclassified	1	0	1
	Benign	15	3	18
	Aggressive	0	22	22
	Total	16	25	41

TABLE 4. Patients who was missed aggressive cranial dural arteriovenous fistulas (DAVFs) from noninvasive imagings.

No	Age (y) /sex	Symptoms	Studies	Locations from DSA	Venous drainages		Dilate of cortical vein	
					CT/MRI	DSA	CT/MRI	DSA
1	45/F	Lt. eye chemosis	CECT	Lt. CS	Lt. SOV	Lt. SOV, Rt SMCV	None	Rt. SMCV
2	77/F	Rt. Lateral rectus palsy	CECT	Rt. CS	Rt. SOV	Rt. SOV, Rt. SPS, Rt. SMCV	None	Rt. SMCV
3	44/M	Rt. 3rd nerve palsy	CECT	Bilat. TS	Bilat. SOV	Bilat. SOV, StS, posterior 1/3 of SSS	None	None
4	75/M	Rt. eye chemosis	CECT	Rt. CS	Rt. SOV	Rt. SOV, Rt. SMCV	None	Rt. SMCV
5	54/M	Pulsatile tinnitus	MRA	Lt. TS	Lt. IJV	Lt.TS, Rt.TS	None	None
6	49/M	Pulsatile tinnitus	MRA	Lt. TS	Lt. IJV	Lt.TS, Rt.TS	None	None
7	42/M	Headache	MRA	Rt. CS	Rt. SOV	Rt.SOV, Rt.SMCV	None	Rt. SMCV

Abbreviations: DSA = digital subtraction angiography, CECT = contrast enhanced CT, MRA = Magnetic Resonance Angiography, bilat = bilateral, CS = cavernous sinus, TS = transvers sinus, SS = sigmoid sinus, StS = straight sinus, IJV = internal jugular vein, IPS = inferior petrosal sinus, SPS = superior petrosal vein, SOV = superior ophthalmic vein, SSS = superior sagittal sinus, SMCV = superficial middle cerebral vein

One patient who was misinterpreted of DAVF, but false positive of sinus thrombosis by CECT, the cerebral angiography revealed a shunt with location at right sigmoid sinus, supplied from trans-osseous branches of right occipital artery. No thrombus in the right sigmoid sinus was identified, although the affected sinus was not visualized as normal venous emptying channel from normal brain circulation, because it had been already occupied by higher blood pressure from the arteriovenous shunts. The filling defect at the sigmoid sinus seen on CT scan might result from artifact of flow competition. In addition, the transosseous arteries supplying the shunts which were overlapped with the cranial vault could not be recognized from CT scan. (Fig 4) The hybrid CT angiography has been reported to have a higher sensitivity and specificity in the diagnosis of DAVFs by using bone removal technique which may provide more advantage for demonstrations of vascular details near skull base and bony structure.[15]

In the other 3 cases with absent criteria of DAVFs, the cerebral angiogram revealed both antegraded and retrograded sinus drainage. All had no CVD, and particularly, no dilatation of the SOV in the case with cavernous DAVF. Furthermore, each affected sinus showed symmetrical appearance on the opposite side. No sinus thrombosis was identified. Thus, CT scan could not recognize DAVFs, because there was no morphologic change of those venous structures. In addition, the visualization of transosseous arterial feeders, which were not significantly dilated, through the cranial vault was also difficult, by spatial and temporal resolution of CT scan. Although there were reports that MRA could improve the identification rate of DAVFs by recognizing flow-related enhancement in the cavernous sinus, and also correctly interpreting posterior drainage in those without anterior drain to superior ophthalmic vein.[18,20-21]

For the characterization of DAVFs, the location at cavernous sinus which was the most common locations

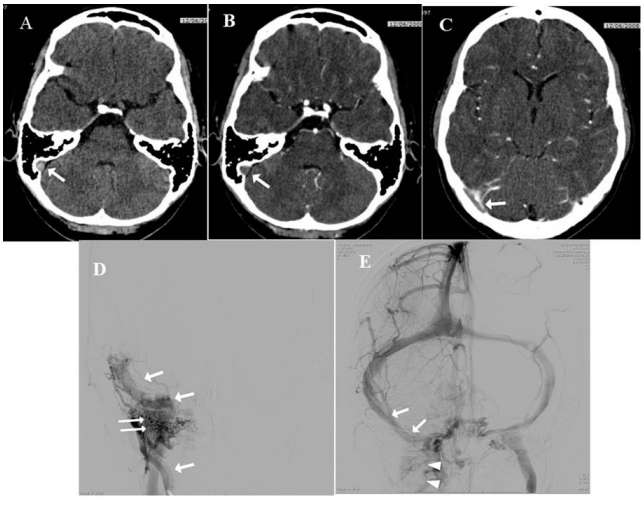


Fig 4. Aggressive cranial dural arteriovenous fistula (DAVF) in a 35-year-old female, presenting with headache was missed diagnosis from CT scan **(A)** Noncontrast enhanced Computed Tomography (NCCT) showed high density blood at the right sigmoid sinus (arrow) **(B) and (C)** contrast enhanced Computed Tomography (CECT) revealed corresponding filling defect at the sigmoid sinus(arrows) (D) Right external carotid angiography frontal view demonstrated DAVF at distal sigmoid sinus to internal jugular vein junction supplying by small trans-osseous branches of occipital artery (small long arrows) with both antegraded and retrograded drainage in the internal jugular vein and proximal sigmoid sinus respectively (arrows) **(E)** Venous phase of right internal carotid angiography frontal view exhibited no visualized distal sigmoid sinus (arrows) and internal jugular vein (arrowheads), which was "functional thrombosis" phenomenon.

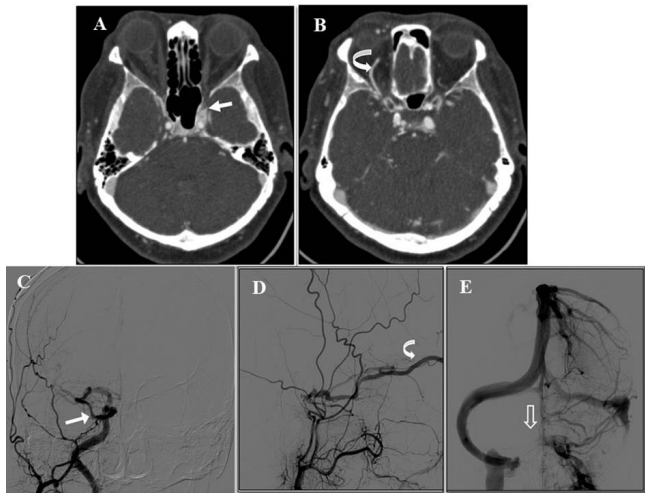


Fig 5. Right cavernous cranial dural arteriovenous fistula (DAVF), benign type, with right cavernous sinus thrombosis. **(A) and (B)** Contrast enhanced Computed Tomography (CECT) revealed prominent left cavernous sinus (arrow) as compared to the right and dilatation of the right superior ophthalmic vein (SOV) (curved arrow) On the basis of visualized sinus morphology, the cranial dural arteriovenous fistula (DAVF) was interpreted to be on the left side. **(C)** Frontal and **(D)** lateral views of right external carotid angiography demonstrated shunt location at the outlet of right superior ophthalmic vein (SOV) **(E)** Note no filling of right cavernous sinus on frontal projection of right internal carotid angiography (arrow) indicative of right cavernous thrombosis.

of our DAVFs, was the most accurate detected from these noninvasive imagings. The most helpful sign for localization was dilatation of the SOV.

Conversely, the lateralization of cavernous sinus location of DAVFs might have some difficulty, because the dilatation of SOV could present on the opposite side to the shunt or even bilaterally. It revealed an interesting pitfall in our study. The patient was demonstrated on cerebral angiography to have DAVF at right cavernous sinus where it had partially thrombosed, and the left cavernous sinus was slightly more prominent than the involved one. On CT images, although the right SOV was larger, the cavernous sinus morphology misled to place the lesion on the left side. (Fig 5) There were previous studies which reported that only a half of carotid-cavernous fistulas detected on contrast-enhanced CT, showed focal or diffuse bulging of the involved side. In contrast to superior ophthalmic vein, it was more frequently observed on the same side as the shunt, in 86%-100% and 75-100% on contrasted CT and conventional MR, respectively.[21-25]

Although shunt locations and multiplicity of the disease were not depicted by the noninvasive imaging tool, it did not change the decision making, once diagnosis of DAVFs were documented, cerebral angiogram with treatment consideration would be indicated. In general, patients who had multiple DAVFS would be recognized by the major one which caused the most serious symptom. The rate of correct detection of venous sinus thrombosis in this study was 38%. In previous studies, it was about 50% by CT and MRI with the usefulness of empty delta sign or filling defect on contrast-enhanced study. Nevertheless, other etiologies, such as arachnoid granulations, intrasinus septa, and venous sinus duplication could mimic the filling defect.[26-28]

Regarding the aggressive behavior of DAVFs, dilated and tortuous leptomeningeal or medullary vessels, venous ectasia as well as leptomeningeal or medullary vascular enhancement were used as evidence of cortical venous reflux.[11,20,29,30] Our result revealed diagnostic accuracy of CT scan and MRI to be good with high sensitivity and specificity. The correct interpretation of aggressive DAVFs by CT was 80% sensitivity and specificity, and MR was 78.9% sensitivity and 95.6% specificity, respectively. (Fig 6)

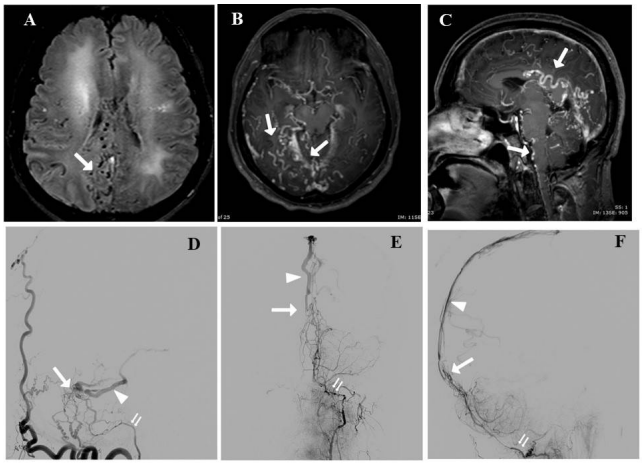


Fig 6. Multiple aggressive type of cranial dural arteriovenous fistula (DAVF) in a 52-year-old man who presented with seizure with incomplete consciousness. **(A)** Magnetic resonance imaging (MRI), axial FLAIR showed abnormal periventricular white matter hypersignal intensity bilaterally with multiple flow voids of cortical venous congestion at right parieto-occipital region (arrow) **(B) and (C)** post gadolinium T1W MRI axial and sagittal views revealed multiple abnormal dilated and tortuous cortical veins including perimesencephalic and spinal cord veins. (arrows). No arterial feeders and sinus thrombosis were identified. (not shown images) The impression was aggressive type of DAVF, however, the site of shunt could not be localized. **(D)** Lateral view of left occipital angiography demonstrated cranial dural arteriovenous fistula (DAVF) at straight sinus (arrow: fistulous point, arrowhead: straight sinus) supplying from tiny emissary branches (small arrows). **(E)** Frontal and **(F)** lateral views of left vertebral angiography demonstrated the 2nd cranial dural arteriovenous fistula (DAVF) at distal 1/3 level of superior sagittal sinus with retrograded drainage fashion. (double small arrows: vertebral artery, arrow: fistulous point, arrowhead: superior sagittal sinus)

Concerning our 7 aggressive DAVFs which were interpreted as benign lesion, 4 cases were cavernous DAVFs, with CVR only into the superficial middle cerebral vein, and they was not dilated enough to be observed from CT or MRI. The other 3 cases were transverse-sigmoid DAVFs with solely retrograded sinus drainage.

CT and MRI could depict the morphology of the dural sinuses and the size of cortical veins, but it was difficult to differentiate the dynamic physiology of venous drainage between DAVFs and normal circulation, particularly with subtle hemodynamic change of the superficial middle cerebral vein. The susceptibility-weighted imaging (SWI) and the time-resolved technique MRI with visible flow direction in different phases, were introduced to overcome the static MRI that benefits not only to determine venous drainage, but also detect small lesions.[31,32]

In our study, the aforementioned findings had emphasized the importance of radiological images in detection of DAVFs, in correlation with clinical presentations, for further planning of endovascular treatment in appropriate time. Those criteria for depiction of DAVFs and their aggressiveness were proved to be applicable on conventional CT and MRI, although there were some limitations for interpretation of the shunt location and multiplicity of the disease.

The limitation of our study was retrospective, single center study with small sample size. The imaging protocol was inhomogeneity and the interpreters were not blinded to the diagnosis of DAVF.

CONCLUSION

The conventional CT and MRI, as available non-invasive diagnostic tools, have shown their capability in detection of DAVFs and identification of the disease aggressiveness. CT or MRI should be used in practice as the initial work up for those symptomatic patients. Nevertheless, diagnostic limitation and misled aggressiveness might be unavoidable in patients who have DAVFs with only dural sinus drainage and no cortical venous reflux. Careful interpretation with clinical correlation are important and helpful for treatment determination in the appropriate time. Cranial angiography should be reserved for patients who require endovascular management and those who have negative imaging result, but present with serious symptoms.

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Characteristics and Neonatal Outcomes of Teenage Pregnant Women Diagnosed with Syphilis at Siriraj Hospital

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ABSTRACT

Objective: To demonstrate the characteristics of teenage pregnant women diagnosed with syphilis during pregnancy and neonatal outcomes.

Methods: This is a retrospective study. Medical records of teenage pregnant women who were diagnosed with syphilis during pregnancy and delivered at Siriraj Hospital and their newborn babies from 2011 to 2016 were reviewed. Demographic data and clinical factors were retrieved. Neonatal outcomes including gestational age at birth, birth weight, and diagnosis of congenital syphilis were recorded. STATA version 12.0 was used to analyze the data and p-value less than 0.05 was considered statistically significant.

Results: During 2011-2016, there were 28 eligible women. The mean age was 17.6±1.2 years. Seventy-five percent of them were unemployed and one-fourth had been educated less than or up to primary school level. The median number of partners was 4 and their sexual debut started from the age of 15.3±0.9. A quarter also had other sexually transmitted infections (STIs). Congenital syphilis was diagnosed in 12 newborns (12/28, 42.8%). The mothers of the newborns with congenital syphilis were more likely to be unemployed, had first antenatal care (ANC) after 20 weeks of gestation, had <4 ANC visits, had high initial non-treponemal titer and poor treatment of syphilis before deliveries ($p<0.05$ for all). Preterm birth and very low birth weight were significantly more common in newborns with congenital syphilis.

Conclusion: Some socio-economic factors are associated with the risk of syphilis infection. Almost half of the teenage pregnant women diagnosed with syphilis delivered babies with congenital syphilis. Inadequate antenatal care and poor treatment of maternal syphilis are the predictive factors of congenital syphilis.

Keywords: Teenage pregnancy; pregnancy outcomes; syphilis (Siriraj Med J 2018;70: 298-301)

INTRODUCTION

Teenage pregnancy, or pregnancy during the age of 10-19 years, is a global health concern. According to World Health Organization, the estimation of pregnancy and childbirth among teenagers is 17 million per year, especially in developing and underdeveloped countries.[1] In Thailand, from 1992 to 2013, the incidence of teenage pregnancy has increased from 0.6 to 1.7 and 40.7 to 51.2 per 1,000 pregnancies in the age group of 10-14 years and in that of 15-19 years, respectively.[2]

Teenage pregnancy prevention is currently one of the national priorities due to its medical and socioeconomic consequences. Among this population, the maternal health risks such as urinary tract infection, preterm labor, preeclampsia, anemia, sexually transmitted infections (STIs) and postpartum depression are prevalent.[1,3] In addition, fetal complications occur more commonly, including fetal growth restriction, low birth weight, neonatal infection and stillbirth.[3] Also, long-term social problems such as unqualified education and career, child

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abuse and low socioeconomic status have been reported.[1,3] Moreover, the daughters of teenage pregnancies are more likely to be teenage mothers themselves.[1]

Teenage mothers are prone to have STIs because of limited sexual education and lack of awareness that STIs may lead to long-term sequelae.[4] Syphilis, a bacterial STI caused by *Treponema pallidum subsp. pallidum*, has shown obvious impact on pregnancy, especially during early stage.[5-9] Half of untreated pregnancies affected by syphilis have early fetal loss/ stillbirth, neonatal death, prematurity/ low birth weight or clinical evidence of syphilis in newborns.[10] In Thailand, although the prevalence of syphilis was 2.8-3.6 per100,000 during 2009-2012, the incidence of congenital syphilis was as high as 10 per 100,000 live births.[11]

As the population of interest is in the age of sex debut, they are at risk for having the early stage of syphilis. Thus, the study aimed to describe the characteristics of teenage pregnancy with first-time diagnosis of syphilis and pregnancy outcomes.

MATERIALS AND METHODS

The descriptive study was approved by the Siriraj Institutional Review Board. (Si 481/2017) The study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Twenty-eight medical records of teenage pregnant women diagnosed with syphilis during 2011-2016 and those of their newborns were reviewed.

Pregnant women aged less than 19 years, diagnosed with any stages of syphilis and giving birth at Siriraj Hospital were included. Women with a past history of syphilis were excluded. Demographic data including maternal age at time of diagnosis, parity, age of sex debut, number of partners, STIs in both women and their partners and antenatal care (ANC) history were collected. Stages and treatment of syphilis were also recorded.

In accordance with Thai National Guideline to eliminate congenital syphilis[11], maternal syphilis was diagnosed using clinical signs and seropositivity of both treponemal and non-treponemal antibodies. Venereal disease research laboratory (VDRL) and *Treponema pallidum* hemagglutination (TPHA) were used in our setting. A single dose of benzathine penicillin G 2.4 million units was used for early stage of syphilis and three doses of benzathine penicillin G 2.4 million units were for late stage of syphilis treatment. Serological follow-up using VDRL was suggested at 1, 3, 6 and 12 months after the treatment. Incomplete treatment or delivery within four weeks after treatment was considered as 'poor treatment'.

Preterm birth was defined as delivery before completion of 37 weeks of gestation. Low birthweight and very low birthweight were classified by neonatal birthweight of less than 2,500 and 1,500 grams, respectively. Birth asphyxia was defined as Apgar score at 1 or 5 minutes was lower than 7.

All newborns were followed up at 2, 4, 6, 9 and 12 months. To diagnose congenital syphilis, cerebro-spinal fluid (CSF) analysis for VDRL, cell count and protein; blood for complete blood count (CBC) for platelet counting and liver function test; long bones radiographs; chest x-rays; neuroimaging; ophthalmologic examination and auditory test were performed after birth.[7,12,13] Newborns are classified into proven or highly suspicious for congenital syphilis when one of the criteria is met. Those who are born to mother with inadequate or no treatment of syphilis, had abnormal physical examination or investigative findings, or had a 4-fold serum titer of nontreponemal test more than the mother's titer, or had a positive dark-field test or PCR in lesions or body fluids.

Statistical analysis

STATA version 12.0 (StataCorp LP, College Station, TX, USA) was used. Descriptive statistics, as well as Chi-square test, student t-test or Wilcoxon rank sum test, were used as appropriate. *P* value <0.05 was considered statistically significant.

RESULTS

During 2011-2016, 28 teenage pregnant women were diagnosed with syphilis and gave birth at Siriraj Hospital. The mean age was 17.8±1.1 years. Most of them were unemployed and one forth had been educated to only primary school level. The median number of partners was 4[2-6] and their sex debut started from the age of 15.3±0.9 years. A quarter also had other sexually transmitted infections (STIs), including 1 human immunodeficiency virus (HIV), 1 hepatitis B, 1 genital herpes, 2 condyloma accuminata and 2 trichomoniasis.

The average gestational age at birth was 36.5±4.2 weeks of gestation. Seventy-eight percent were delivered vaginally and all of them were alive at birth. The mean birth weight was 2,553±800 grams with nearly 40 percent being in low birth weight range. There were nine newborns who were diagnosed as birth asphyxia. Congenital syphilis was found in 12 newborns (12/28, 42.8%). Three of them had neurosyphilis.

The mothers of newborns with congenital syphilis were more likely to be unemployed, had the first ANC after 20-week gestation, had ANC <4 visits, had high initial non-treponemal titer and had poor treatment

of syphilis before delivery ($p<0.05$ for all). Preterm birth and very low birth weight were more common in newborns with congenital syphilis, at 75.0% vs 12.5%, $p = 0.001$; and 33.3% vs 0.0%, $p = 0.013$.

DISCUSSION

Teenage women are vulnerable to STIs owing to their immature immune status which becomes worse during pregnancy. In addition, compatible with previous studies[4,6,9], low socio-economic status and education, emotional immaturity, poor psychological well-being and ANC as well as multiple sex partners are commonly found. As a consequence, the present study has demonstrated that half of teenage pregnant women with syphilis give birth to infected newborns.

Nowadays, the prevalence of teenage pregnancy in Siriraj Hospital accounts for 7-8%.[14,15] Compared with pregnancies in other age groups, they are more likely to have multiple partners, co-incidental STIs, inadequate treatment before delivery, preterm birth and low birth weight.[16] Therefore, teenagers who get pregnant should be taken care of in the high-risk pregnancy clinics run by a multidisciplinary care team: obstetricians, pediatricians, psychiatrists and social workers. A sexual health policy in adolescents should be established and health education needs to be emphasized and spread among teenagers both in school and mass media.

According to Annual reports from 2015 to 2016 of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, the prevalence of maternal syphilis in teenage was 1.27% compare to 0.6% in overall pregnant women.[14,15] Previous studies showed that the prevalence of maternal syphilis varied by global regions. In European countries and the United States, the prevalence was 0.02-4.5% while that in Africa was 3-18%.[8,17] However, the common characteristics were teenage pregnancy and being unmarried.

Newborns of untreated maternal syphilis are likely to be infected, especially in mothers with early syphilis.[6,9,18] The present study showed that almost half of the newborns had congenital syphilis. The high incidence can be explained by the fact that these pregnant women had just started sexual activities and, most likely, practicing unprotected sex. As a consequence, most of them were in early stage of syphilis, but might be asymptomatic. Blood test for STIs during pregnancy in this high-risk population should be compulsory.

The strength of this study was the complete medical recording of the participants and their newborns of whom STI specialists took care. The main limitation was the small sample size as the study population was a specific group. Besides, the present study focused on only intra-partal and post-partal pregnancy outcomes, so the adverse outcomes during early pregnancy were not included. A prospective study on teenage pregnancy from the first ANC visit and outcomes of neonatal follow-up will better depict the impact of syphilis on pregnancy of this special population.

CONCLUSION

Around half of newborns of teenage pregnant women diagnosed with syphilis at Siriraj Hospital between 2011 and 2016 had congenital syphilis. Inadequate antenatal care and poor treatment of maternal syphilis are the predictive factors. This emphasizes the importance of sexual health education in teenage population.

TABLE 1. Characteristics of teenage pregnancies with syphilis by neonatal outcomes at Siriraj Hospital during 2011-2016.

Characteristic	Total (N=28)	Congenital syphilis (N = 12)	No congenital syphilis (N= 16)	*P*-value
Age (years)	17.8±1.1	17.5 [16.7-18.2]	18.2 [17.7-18.9]	0.169
No education/Primary school	7 (25.0)	5 (41.7)	2 (12.5)	0.078
Being unemployed	21 (75.0)	12 (100.0)	9 (56.3)	0.008
Age of sex debut (years)	15.3±0.9	15.3±1.1	15.3±0.9	0.955
Number of partners	4 [2-6]	4 [2-5]	5 [2-7]	0.233
Coincidence with other STIs	7 (25.0)	3 (25.0)	4 (25.0)	1.000
Nulliparity	21 (75.0)	10 (83.3)	11 (68.8)	0.378
GA at the first ANC (weeks)	19.1±7.7	23.8±7.5	15.5±6.0	0.003
First ANC after GA 20 weeks	12 (42.9)	8 (66.7)	4 (25.0)	0.027
ANC < 4 visits	8 (28.6)	8 (66.7)	0 (0.0)	<0.001

TABLE 1. Characteristics of teenage pregnancies with syphilis by neonatal outcomes at Siriraj Hospital during 2011-2016. (Cont.)

Characteristic	Total (N=28)	Congenital syphilis (N = 12)	No congenital syphilis (N= 16)	*P*-value
GA at diagnosis of syphilis (weeks)	19.8±7.8	24.5±8.1	16.4±5.7	0.004
Initial VDRL titer ≥ 1:8	25 (89.3)	12 (100.0)	13 (81.3)	0.112
Initial VDRL titer ≥ 1:16	19 (67.9)	11 (91.7)	8 (50.0)	0.019
Incomplete/ no treatment or complete treatment <4 weeks before delivery	10 (35.7)	10 (83.3)	0 (0.0)	<0.001
Partner tested for syphilis	22 (78.6)	8 (66.7)	14 (87.5)	0.184
Partner treated for syphilis (N= 22)	11 (39.3)	6/8 (75.0)	5/14 (35.7)	0.076
GA at delivery (weeks)	36.5±4.7	33.6±4.7	38.7±1.7	<0.001
Delivery before 37 weeks	11 (39.3)	9 (75.0)	2 (12.5)	0.001
Delivery before 34 weeks	6 (21.4)	6 (50.0)	0 (0.0)	0.001
Newborn's birth weight (grams)	2,553±800	2,091±907	2,898±502	0.006
Birthweight <2,500 g	11 (39.3)	7 (58.3)	4 (25.0)	0.074
Birthweight <1,500 g	4 (14.3)	4 (33.3)	0 (0.0)	0.013
Birth asphyxia	9 (32.1)	6 (50.0)	3 (18.6)	0.080

Data presented in N (%) or mean±S.D. or median [IQR]

Abbreviations: ANC = antenatal care, Birth asphyxia = Apgar score ≤7 at 1 or 5 minutes, GA = gestational age, STIs = sexual transmitted infections

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The Relationships among Objective Measures of Tongue Strength and Risk of Aspiration

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ABSTRACT

Objective: The objective measures of tongue strength can predict the risk of aspiration. Isometric tongue pressure and endurance have been reported to be lower in patients who have premature spillage, penetration and/or aspiration on endoscopic evaluation. We aimed to study the relationships between the objective measures of tongue strength and risk of aspiration in our population.

Methods: Seventy-five participants were enrolled to the study. The mean age of the participants was 58.3 ±13.6 years old. They were divided into three groups (25 participants in each group). The first group was normal participants who have had no history of swallowing problem with normal flexible endoscopic evaluation of swallowing (FEES). The second group was symptomatic patients who have had history of dysphagia and/or aspiration but normal FEES. The third group was patients who have had history of dysphagia and/or aspiration with evidence of premature spillage or laryngeal penetration or aspiration by FEES. All participants underwent objective measurements of the tongue strength including maximal isometric pressure (MIP) and endurance by Iowa Oral Performance Instrument (IOPI). The quantitative data between groups were compared using ANOVA and chi-square test was used for qualitative data. The optimal cut-off points were determined by Receiver Operating Characteristic (ROC) curve.

Results: MIP and endurance were significantly lower in patients who have had premature spillage, penetration and/or aspiration on endoscopic evaluation. The appropriate cut-off points for high risk group are 35 and 25 kPa for the anterior and posterior tongue pressure respectively.

Conclusion: The tongue pressure can be used to screen patients who are at risk of aspiration, which will lead to early investigation and intervention for the management of these patients.

Keywords: Tongue pressure; Iowa Oral Performance Instrument (IOPI); flexible endoscopic evaluation of swallowing (FEES) (Siriraj Med J 2018;70: 302-309)

INTRODUCTION

The tongue is an important key structure for bolus formation and generating pressure for bolus propelling.[1-3] The impairment of lingual function exhibits reduction of bolus control, resulting in spillage or leakage of the food from the oral cavity into the pharynx before swallowing. The patients will ultimately have severe laryngeal penetration and aspiration. Aspiration can cause pneumonia, lung abscess, and fatal respiratory failure.[4-6] Patients at risk of severe premature spillage include elderly patients, patients with neuromuscular diseases such as stroke, Parkinson's disease, myasthenia gravis, or multiple sclerosis etcetera.[5] Leder found that patients who had incomplete lingual range of motion had 2.72 times higher risk of aspiration than a person without this problem.[7] Many clinicians use tongue-strength testing to determine potential risk of aspiration. Iowa Oral Performance Instrument (IOPI®) is a tool that is used to measure the strength of the tongue. This is a standard and reliable tool as has been shown in many researches.[1,3,8-12] The objective of this study was to

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determine degree of tongue weakness with the risk of premature spillage which could lead to severe aspiration, and the tongue pressure in normal Thai population.

MATERIALS AND METHODS

This study was performed between August 2014 and April 2016 after being approved by the Human Investigation Committee. Measures of tongue strength were collected from three groups of individuals.

Population

1. **The first group** (normal participants group, n=25) had no history of swallowing problem and normal flexible endoscopic evaluation of swallowing (FEES)
2. **The second group** (symptomatic group, n=25) had history of dysphagia and aspiration that interfered with daily life and needed medical attention, but had normal FEES (no evidence of premature spillage or laryngeal penetration or aspiration).
3. **The third group** (diseased group, n=25) had history of dysphagia and aspiration with evidence of premature spillage or laryngeal penetration or aspiration on FEES.

Instrumentation & Intervention

Determining of aspiration status

The aspiration status of all participants was obtained by FEES. (Fig 1) The main findings of interest were premature spillage, laryngeal penetration, and aspiration.

1. **Premature spillage** is defined as inability to hold the food bolus within the oral cavity before initiating the pharyngeal phase of swallowing.
2. **Laryngeal** penetration is defined as passage of materials into the larynx, but not through the vocal folds.
3. **Aspiration** is defined as passage of materials through the vocal folds.



Fig 1. FEES instruments and FEES technique.

Measures of tongue strength

The tongue strength was objectively assessed by IOPI. (Fig 2) We placed the bulb on anterior tongue (just behind the alveolar ridge) and posterior tongue (midline of the tongue at sulcus terminalis) and then measured the following two values; (Fig 3)

1. **Maximum isometric pressure (MIP)** is the highest pressure that occurs when a patient's tongue is pushed against the palate. The MIP is reported in kilopascals (kPa).
2. **Endurance** is the period that a patient can maintain the pressure about 50% of the MIP, measured in seconds. This value represents the exhaustion of the tongue or tongue fatigability.



Fig 2. IOPI (Iowa oral performance instrument).

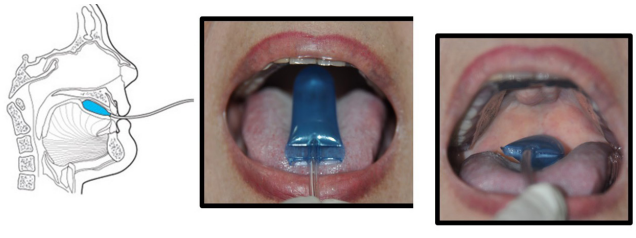


Fig 3. Position of tongue bulb.

Analysis

Statistical analyses have been conducted using SPSS version 19 (SPSS Inc). Descriptive statistics including the number & percentage of the categorical data and mean ± standard deviation of the continuous data with normal distribution were calculated to examine the distribution characteristics of group performance on tongue measures. All between-group comparisons were investigated using ANOVA for quantitative data (tongue measures, age) and chi-square test for qualitative data (sex). Pearson correlation was used to explore the relationship of tongue measure and bulb location. The

optimal cutoff points were determined using Receiver Operating Characteristic (ROC) curves and diagnostic values (sensitivity, specificity, positive and negative predictive values) were calculated. Significance level was set at 0.05 for all analyses.

RESULTS

Seventy-five adults were enrolled in this study. The mean age was 58.3 ±13.6 years (ranged 30-85), which did not differ between groups. Eleven of 50 patients (22%) with dysphagia had a history of aspiration pneumonia at least once in life. When compared with symptomatic group, the diseased group had more incidence of this event (40 vs. 4%). The most common underlying disease was cerebrovascular disease which was found 64% in the diseased group.

Descriptive statistics including age, gender, underlying disease, history of aspiration pneumonia, and duration of symptom are shown in Table 1.

Isometric tongue strength by objective measurement

The mean anterior isometric tongue strength in diseased group was 19.9±11.1 kPa (95% CI 15.3-24.5), which was significantly less than that of the normal participant group (59.5±13.3 kPa, 95% CI 54.0-65.0, $P < .001$) and the symptomatic group (46.4±10.4 kPa, 95% CI 42.1-50.7, $P < .001$). When comparing the mean posterior isometric tongue strength, we found the similar result that diseased group had lower posterior tongue strength than both normal participants (12.8±7.5, 95% CI 9.7-15.9 vs. 54.0±12.6, 95% CI 48.8-59.2, $P < .001$) and symptomatic group (12.8±7.5, 95% CI 9.7-15.9 vs. 39.4±12.7, 95% CI 34.1-44.6, $P < .001$). Moreover, the symptomatic group also had significantly lower isometric tongue strength than the normal participants on both anterior (46.4±10.4 vs. 59.5±13.3 kPa, $P < .001$) and posterior (39.4±12.7 vs. 54.0±12.6 kPa, $P < .001$) bulb location. (Table 2)

Correlation between anterior vs. posterior isometric tongue strength

Anterior isometric tongue strength was positively correlated with posterior isometric tongue strength (r= 0.915, $P < .001$), as shown in Fig 4.

From the ROC curve, the anterior and posterior isometric tongue strength cutoff values that were the best fit to identify aspiration in FEES were 35 and 25 kPa respectively. At this cutoff, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 92% (95% CI 75-98%), 96% (95% CI 87-99%), 92% (95% CI 75-98%) and 96% (95% CI 87-99%) respectively. The accuracy was 94.7% (95% CI 87-98%). By using the forward stepwise logistic regression analysis, we observed an increased risk for aspiration among who had anterior isometric tongue strength less than 35 kPa or posterior isometric tongue strength less than 25 kPa (Diagnostic Odd Ratio (DOR) 65.01; 95% CI 5.02-841.72) as shown in Fig 5.

TABLE 1. Demographics characteristic of 75 studied participants.

	Total (n=75)	Normal participant (n=25)	With dysphagia symptoms		*P* value**
			Normal FEES* (n=25)	Abnormal FEES* (n=25)	
Gender					
Male	45 (60%)	14 (56%)	14 (56%)	17 (68%)	0.607
Female	30 (40%)	11 (44%)	11 (44%)	8 (32%)	
Mean age (year) ± SD	58.3±13.6	53.8±13.8	59.9±12.7	61.2±13.6	0.117
Has history of aspiration pneumonia	11 (14.6%)	-	1 (4%)	10 (40%)	N/A
Mean duration of dysphagia (days)	206.2±166.2	-	205.0±158.8	207.4±176.5	N/A
Neurological diseases (e.g. CVA)	22 (29.3%)	0	6 (24%)	16 (64%)	N/A

*Normal FEES: defined as no evidence of premature spillage, laryngeal penetration and aspiration on FEES Abnormal FEES: defined as present of premature spillage or laryngeal penetration or aspiration on FEES

**The mean difference is significant at the 0.05 level.

Abbreviations: CVA = cerebrovascular accident, N/A = not applicable

TABLE 2. Mean anterior and posterior isometric tongue strength obtained on the IOPI.

	Normal Participant (n=25)	With dysphagia symptoms		*P* value ***
		Normal FEES * (n= 25)	Abnormal FEES * (n= 25)	
Anterior tongue strength (kPa)**	59.5±13.3 (35.0-86.0)	46.4±10.4 (23.0-69.0)	19.9±11.1 (4.0-48.0)	< .001[a]
Posterior tongue strength (kPa)**	54.0±12.6 (30.0-76.0)	39.4±12.7 (22.0-69.0)	12.8±7.5 (2.0-29.0)	< .001[a]

*Normal FEES: defined as no evidence of premature spillage, laryngeal penetration and aspiration on FEES Abnormal FEES: defined as present of premature spillage or laryngeal penetration or aspiration on FEES
** Mean±SD (minimum-maximum)
*** The mean difference is significant at the 0.05 level.
a: Using ANOVA and Bonferroni analysis methods, all pairwise comparisons had significantly differentiation (*P*< .05)

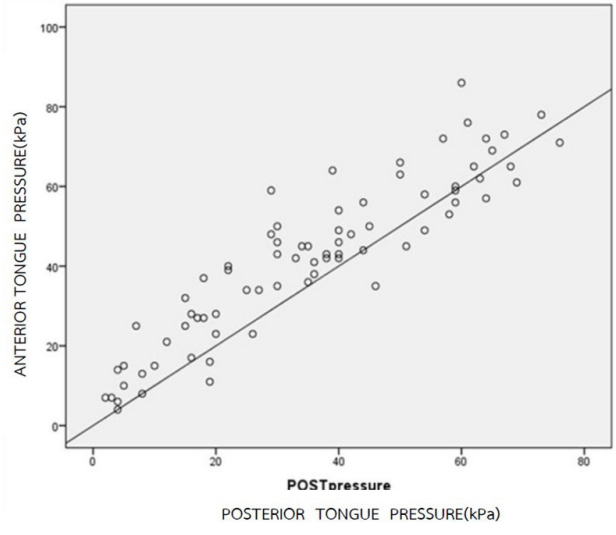


Fig 4. Correlation between anterior and posterior tongue pressure. Circle dots indicate individual data points.

Isometric Endurance

The mean isometric endurance in the diseased group was significantly less than the two other groups at both anterior (2.7±2.5; 95% CI 1.6-3.7 vs. 10.6±4.1; 95% CI 8.9-12.3, *P* < .001 and 2.7±2.5; 95% CI 1.6-3.7 vs. 7.9±4.7; 95% CI 5.9-9.8, *P* < .001) and posterior (1.7±1.9; 95% CI 0.9-2.5 vs. 9.8±4.8; 95% CI 7.8-11.7, *P* < .001 and 1.7±1.9; 95% CI 0.9-2.5 vs. 5.8±2.9; 95% CI 4.6-7.0, *P* < .001) bulb location. The same result was found when anterior and posterior endurances were compared between normal participants and symptomatic group (10.6±4.1 vs. 7.9±4.7, *P* = .048 and 9.8±4.8 vs. 5.8±2.9, *P* < .001). The mean anterior and posterior isometric endurances in all groups were illustrated in Table 3.

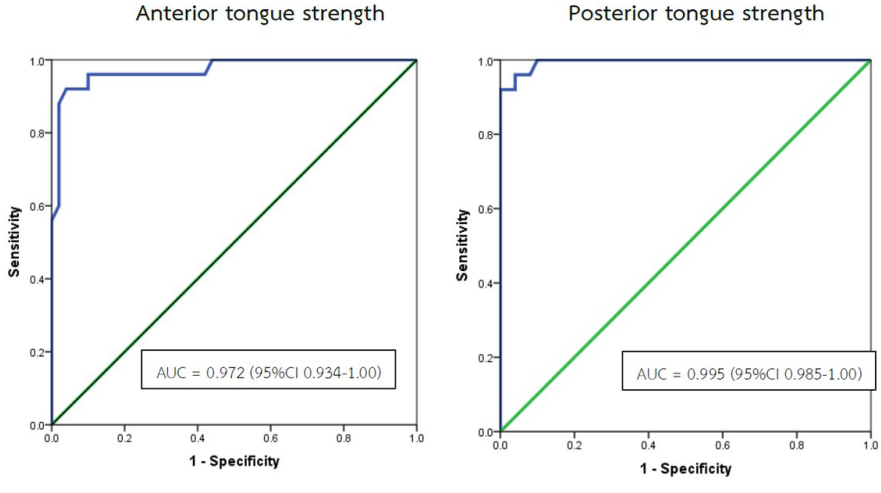


Fig 5. Receiver Operating Characteristic curves (ROC curve) of anterior and posterior isometric tongue strength to identify aspiration by FEES in all studied patients.

TABLE 3. Mean anterior and posterior endurance obtained on the IOPI.

	Normal	With dysphagia symptoms		
	Participant (n=25)	Normal FEES * (n= 25)	Abnormal FEES * (n= 25)	*P* value***
Anterior endurance (sec)**	10.6±4.1 (4.0-18.0)	7.9±4.7 (1.0-23.0)	2.7±2.5 (0-8.0)	< .001[a]
Posterior endurance (sec)**	9.8±4.8 (3.0-20.0)	5.8±2.9 (1.0-12.0)	1.7±1.9 (0-7.0)	< .001[a]

*Normal FEES: defined as no evidence of premature spillage, laryngeal penetration and aspiration on FEES Abnormal FEES: defined as present of premature spillage or laryngeal penetration or aspiration on FEES

** Mean ± SD (minimum-maximum)

*** The mean difference is significant at the 0.05 level.

a: Using ANOVA and Bonferroni analysis methods, all pairwise comparisons had significantly differentiation ($P < .05$)

Correlation between anterior vs. posterior endurance

There was a significant correlation between anterior endurance and posterior endurance (r= 0.830, $P < .001$), as shown in Fig 6.

The areas under the ROC curve to differentiate the aspiration-positive on FEES and aspiration-negative group using anterior and posterior endurances were 0.901 and 0.927 respectively. The cutoff point of 8 secs for anterior isometric endurance and 3 secs for posterior isometric endurance yielded the highest sensitivity and specificity. At this cutoff, the sensitivity, specificity, PPV, NPV, and accuracy of the anterior part were 96% (95% CI 80-99%), 66% (95% CI 52-77%), 58.5% (95% CI 43-72%), 97.1% (95% CI 85-99%), and 76% (95% CI 65-84%) respectively, and for the posterior part were 72% (95% CI 52-85%), 94% (95% CI 84-98%), 86% (95% CI 65-95%), 87% (95% CI 76-94%), and 86% (95% CI 77-92%) respectively, as shown in Fig 7.

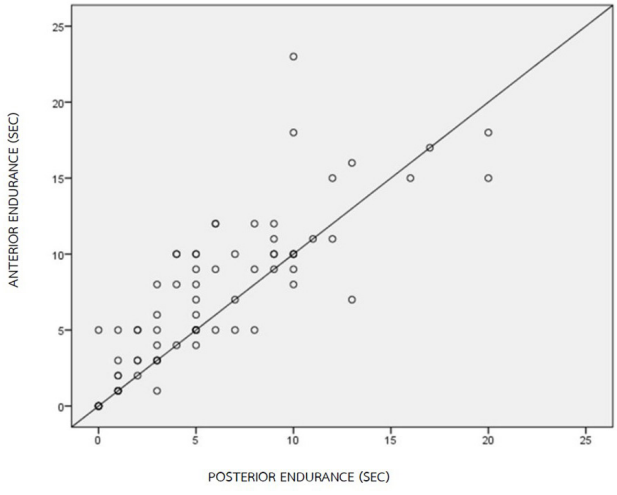


Fig 6. Correlation between anterior and posterior endurance.

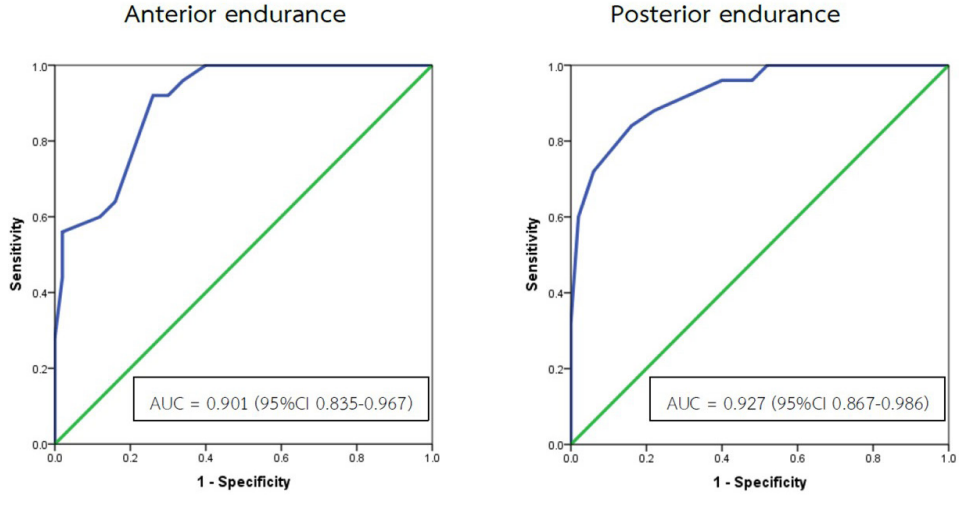


Fig 7. Receiver Operating Characteristic curves (ROC curve) of anterior and posterior endurance to identify aspiration in FEES in all studied patients.

Tongue strength and endurance in normal population

The mean and SD of anterior and posterior isometric tongue pressures obtained from the 25 control participants were 59.5±13.3 (95% CI 54.0-65.0) and 54.0±12.6 (95% CI 48.8-59.2) kPa respectively, whilst the anterior and posterior endurances were 10.6±4.1 (95% CI 8.9-12.3) and 9.8±4.8 (95% CI 7.8-11.7) secs respectively.

Effect of age and sex on the isometric tongue strength and endurance

Men were more likely to have higher isometric tongue strength than women with both anterior (63.8 vs. 54.1) and posterior (58.6 vs. 48.1) bulb location, but only the difference of posterior tongue strength was significant (P = .035). As well as the endurance, men tended to have longer endurances at both anterior (11.4 vs. 9.5) and posterior (11.0 vs. 8.2) bulb locations, but the difference was not significant (P >.05). To compare between two age groups: <60 years and ≥60 years, the result revealed that younger group had stronger tongue strength and higher endurance than the elder, but this was not statistically significant. This study revealed no correlation between age and isometric tongue strength or age and endurance in healthy participants. (Table 4)

DISCUSSION

Dysphagia accounts for approximately 24% to 80% of patients which depends on the concomitant medical disorders and the population studied.[6,13] Dysphagia is practically classified into two categories; oropharyngeal and esophageal dysphagia. Tongue weakness implies one of the common etiologies of oropharyngeal dysphagia, which leads to chronic aspiration.[2,6,14-16] In our study, 22% of patients with clinical dysphagia had a meaningful aspiration resulting in aspiration pneumonia at least once in life. Leder found that patients with impaired lingual function would have a 2.72 times higher risk of aspiration than a person without this problem.[7] Our result shows that patients who have had laryngeal penetration-aspiration had lower isometric tongue strength at both anterior and posterior bulb locations compared with normal participants. These support findings of previous studies that lower isometric tongue strength represented diminished functional reserve, which increased risk for dysphagia and aspiration.[1,3,17] The impairment of lingual function reduces ability to maintain the bolus during the oral phase and leads to spillage or leakage of the food from the oral cavity into the pharynx before airway protection reflex occurs. The suitable tongue strength is essential for safe swallowing and the exercises designed to strengthen the tongue may be one of the most useful therapies.[18] Common assessment is based on subjective judgment of the force being applied by tongue against resistance provided by tongue depressor. Disadvantages of subjective method are assessors' bias and inconsistent grading by multiple assessors.[9] Isometric endurance is another interesting value that represents fatigability of tongue. During the oral phase, the tongue creates the pressure against the palate to seal the posterior exit. If a patient can hold the pressure only shortly, this will increase the likelihood of leakage leading to premature spillage and penetration-aspiration. While the relationship

TABLE 4. Mean anterior & posterior tongue strength and anterior & posterior endurance as a function of age and gender in normal participant (n=25)

	Anterior tongue strength (kPa)*	Posterior tongue strength (kPa)*	Anterior endurance (sec)*	Posterior endurance (sec)*
Gender				
Men	63.8±13.2	58.6±11.2	11.4±1.0	11.0±5.3
Women	54.1±11.8	48.1±12.2	9.5±4.2	8.2±3.6
P Value **	.069	.035	.268	.145
Age				
<60	61.8±12.9	55.8±12.1	11.3±3.7	10.6±4.8
≥60	52.3±12.9	48.3±13.5	8.5±5.0	7.0±3.7
P Value **	.132	.214	.159	.104

* Mean±SD

** The mean difference is significant at the 0.05 level.

of strength of tongue and swallowing function are well documented, the study of endurance is limited and the results about this issue are inconsistent. The systematic review of Valerie A et al in 2013 revealed that when compared with healthy control groups, the populations with disorders such as Parkinson's disease, head and neck cancer, multiple sclerosis, traumatic brain injury, or cerebrovascular accident had significantly lower tongue endurance, but they did not identify the aspiration status among patients.[9] Our study revealed that patients who have had laryngeal penetration-aspiration had lower isometric endurance at both anterior and posterior bulb locations compared with normal participants. The IOPI is one of the objective methods that has been used successfully to evaluate tongue strength in several studies.[9,19] Up to date, the cutoff points to identify risk of aspiration on endoscopic evaluation has not been reported. From our study, the most appropriated cutoff points for the anterior and posterior tongue pressures to the presence of aspiration are 35 and 25 kPa, respectively. These scores offer high sensitivity, specificity, positive and negative predictive value and accuracy. Additionally, a patient who has anterior isometric tongue strength less than 35 kPa or posterior isometric tongue strength less than 25 kPa would have 65.01 times higher risk for aspiration than a person who has more tongue strength. These cutoff scores are suitable in screening and grading patients into high or low risk of aspiration. This will allow physicians to better identify those who will benefit from aspiration precautions20 and can help them choose a better treatment plan such as dietary modification, postural adjustment, and/or tongue strengthening rehabilitation. We observed that 6 patients in the diseased group who had received tongue strengthening training exercise developed better isometric tongue strength and ultimately decreased the degree of penetration-aspiration on FEES.

According to tongue strength measures in normal swallowing, mean values of tongue strength is ranged from 43 to 78 kPa in healthy adults[9,21] and the difference of maximal tongue strength and endurance in healthy normal population was reported depending on race and age.[9,22,23] The normal score in Thai population has not previously been studied. Our study demonstrated means of anterior and posterior tongue strengths in healthy Thai people are 59.5±13.3 kPa and 54.0±12.6 kPa respectively. The mean of anterior and posterior endurances are 10.6±4.1 and 9.8±4.8 secs respectively. No statistically significant difference of the tongue strength and endurance between adult men and women was found in this study. Previous literatures mentioned the effect of aging on tongue strength and reported that maximum tongue strength would decrease with increasing age in healthy adults.[9,22,24] They hypothesized that the result was related to an overall decline in skeletal muscle mass and central nervous system change in the elderly.[17] However, this will require further investigation for the tongue pressure and endurance in each gender of varying age groups and races.[25,26] Finally, the positions of the IOPI bulb applied in the mouth may have differed between studies.[27] In this study we recorded the tongue strength and endurance both anteriorly and posteriorly and obtained the similar result that the tongue strength and endurance measured in the anterior position was typically higher than in the posterior part.[9] Nevertheless, there were the positive correlations of both tongue strength and endurance values obtained from the anterior and posterior portions of tongue, so clinicians can measure the tongue pressure only at the anterior part because of the ease of application.

CONCLUSION

Our data suggests that objective measures of tongue strength can predict the risk of aspiration. Isometric tongue strength and endurance were lower in patient who had had premature spillage, penetration and/or aspiration on endoscopic evaluation. Tongue strength measured by IOPI may help identify patients at risk of aspiration and the appropriate cutoff points for high risk group are 35 and 25 kPa for the anterior and posterior tongue pressures respectively. According to its simple techniques, the tongue pressure can be used to screen aging or neurological deficit population which will lead to early investigation and also early intervention especially in the high risk for aspiration group.

ACKNOWLEDGMENTS

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Multiple Primary Malignancies in Gynecologic Cancer Patients in Thai Tertiary Care Center: a 10-Year Retrospective Study

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ABSTRACT

Objective: To investigate the incidence, pathologic features, clinical characteristics, oncologic outcomes, and prognostic factors in gynecologic cancer patients with multiple primary malignant tumors (MPMT).

Methods: This single-center retrospective study included the medical records of gynecologic cancer patients diagnosed with MPMT according to Warren and Gates's criteria who were treated at the Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Siriraj Hospital during January 2006 and December 2016. Relevant demographic, clinical, and pathologic data were collected and analyzed.

Results: Of 8,076 cases of gynecologic cancer during the study period, 146 women with MPMT were included. Ninety-four women had multiple primary gynecologic cancers (MPGC), and 52 had gynecologic cancer coexisting with non-gynecologic cancer (GNC). The prevalence of MPGC was 1.2%. Synchronous cancer, nulliparous, premenopause, and early stage of endometrial and ovarian cancer were significantly more common among MPGC than GNC. Five-year recurrence-free survival (RFS) was significantly longer in the MPGC group (87.3% *vs.* 79.6%). Coexisting endometrial and ovarian cancer was the most frequently observed MPGC, with a 5-year overall survival (OS) and RFS of 98.1% and 86.0%, respectively. Specific to this cancer combination, residual tumor and depth of myometrial invasion were found to be independently associated with shorter RFS.

Conclusion: The prevalence of MPGC in this study was 1.2%. Five-year RFS was significantly longer among MPGC than among GNC. Three-quarters of MPGC patients had synchronous endometrial-ovarian cancer. Residual tumor and the depth of myometrial invasion were identified as prognostic factors that were independently associated with RFS in the patients with synchronous endometrial-ovarian cancer.

Keywords: Clinical characteristics; oncologic outcomes; gynecologic cancer patients; multiple primary malignancies
(Siriraj Med J 2018;70: 310-319)

INTRODUCTION

The condition referred to as multiple primary malignant tumors (MPMT) was first described by Warren and Gates in 1932.[1] The essential criteria for diagnosis of this condition according to Warren and Gates is histopathologic cancer diagnosis in different organs that is not caused by metastasis from the first tumor to one or more subsequent tumors. There are a variety of other definitions of MPMT, but the Warren and Gates definition is the mostly widely accepted and used. Regarding duration between diagnosis date of distinct malignancies, MPMT is classified as either synchronous or metachronous. Diagnosis of both tumors within a 6-month period is termed synchronous, with duration of

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diagnosis between the two tumors longer than 6 months termed metachronous.

The reported prevalence of MPMT varied from 0.4%-21.0% depending on the type of publication and the ethnicity of the study participants.[2-5] Synchronous tumor and metachronous tumor accounted for 34%-38% and 62%-66% of all MPMT, respectively.[2] Specific to gynecologic malignancy, the reported overall prevalence was 1.9%-4.3%.[6,7] The most frequently observed combination of coexisting gynecologic tumors was endometrial and ovarian cancer (81.0%).[8,9] It is possible that the incidence of MPMT may increase as a result of lifespan extension, more effective screening, and the development of improved cancer treatments. Moreover, previous studies reported different characteristics of MPMT compared to those of single primary malignancy, including younger age[9], significantly associated family history[7], typical pathologic features, and better prognosis.[10,11]

Given the increasing trend in the occurrence of MPMT and reported variations in characteristics between MPMT and single primary malignancy, the aim of this study was to investigate the prevalence, pathologic features, clinical characteristics, oncologic outcomes, and prognostic factors in gynecologic cancer patients with MPMT. These results might be helpful in prognification and surveillance plan regarding the risk of second malignancy.

MATERIALS AND METHODS

This single-center retrospective study included the medical records of gynecologic cancer patients diagnosed with multiple primary malignancy tumors (MPMTs) according to Warren and Gates's criteria who were treated at the Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Siriraj Hospital from 1st January 2006 to 31st December 2016 Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 807/2016). Written informed consent was waived due to the retrospective design of this study.

Patient data that were collected included multiple primary gynecologic cancers (MPGC) or gynecologic cancer coexisting with non-gynecologic cancer (GNC), synchronous or metachronous tumor, interval between first and second cancers, cancer site combinations, age at diagnosis of first malignancy, age at diagnosis of cancer at each location, pathologic findings, nulliparous, menopause, family history of malignancy, genetic testing, venous thromboembolism, stage of cancer at each location, complete response, recurrence, death, 5-year overall response, and 5-year recurrence-free response.

Warren and Gates criteria for diagnosis of MPMT are, as follows: 1) Each tumor exhibits evidence of cancer; 2) Each tumor has distinct pathologic feature(s); and, 3) Metastasis or recurrent disease from prior cancer must be excluded.[1] All cases were diagnosed by expert pathologists at our center. Pathologic slides that were used to establish a diagnosis at another hospital were re-evaluated by our expert gynecologic pathologists to confirm diagnosis. The time of diagnosis was the time that histopathologic diagnosis was established. Response rate after receiving primary treatment and time to event (recurrence, death, and/or last follow-up) were calculated. Overall survival (OS) was defined as the interval from the date of initial diagnosis of the specified cancer to the date of death or last follow up. Recurrence-free survival (RFS) was calculated as the interval from the date of initial diagnosis of the specified cancer to the date of recurrence or last follow-up. Patients who were lost to follow-up before they completed primary treatment of either cancer were excluded from this study.

Statistical analysis

All data analyses were performed using PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize demographic and clinical characteristics. Qualitative data are presented as frequency and percentage, and quantitative data are presented as mean ± standard deviation or median and range. Chi-square test (categorical data) and Student's t-test (continuous normally distributed data) were used to compare clinical and pathological data between groups. Kaplan-Meier survival analysis was performed, and the results were compared using log-rank test. Factors associated with survival were analyzed by Cox regression. A p-value less than 0.05 was regarded as being statistically significant.

RESULTS

Of 8,076 cases of gynecologic cancer identified during the 2006 to 2016 study period 7,930 cases were excluded for the following reasons: pathologically proven single primary malignancy (7,730), and loss to follow-up before completion of primary treatment.[11] The remaining 146 women were enrolled in this study. Included subjects were divided into either the multiple primary gynecologic cancers (MPGC) group or the gynecologic cancer coexisting with non-gynecologic cancer (GNC) group.

Multiple primary gynecologic cancers (MPGC)

The prevalence of MPGC in this center was 1.2%. Eighty-six of 94 MPGC cases (91.5%) were synchronous cancer. The most frequently observed coexisting gynecologic tumors were endometrial-ovarian cancer (76.6%), followed by cervical-ovarian cancer (10.6%) and cervical-endometrial cancer (5.3%). The remaining eight patients had metachronous tumors, with a median duration between diagnosis of the first and second cancers of 12.5 years (range: 0.7-24.2), and all of them presented with either cervical or vulvar cancer. The mean age at diagnosis was 53.4, 53.2, and 50.7 years for endometrial, ovarian, and cervical cancers, respectively. Fifty-three (56.3%) of the 94 MPGC women were nulliparous, and 46 (48.9%) were in menopause. Venous thromboembolism was identified in six patients (6.3%). The vast majority of endometrial cancers (92.4%) and ovarian cancers (80.5%) were early-stage. Complete response rate was achieved in 92.4% of cases. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 96.1% (95% confidence interval [CI]: 91.8-100) and 87.3% (95% CI: 79.3-95.3), respectively. Patient characteristics and oncologic outcomes compared between MPGC and GNC are shown in Table 1.

Synchronous endometrial and ovarian cancer

The 72 cases of coexisting endometrial and ovarian cancer accounted for 0.9%, 4.4%, and 3.7% of gynecologic cancer, endometrial cancer, and ovarian cancer, respectively. All 72 cases were synchronous cancer. Mean age at diagnosis was 53.3±10.3 years. Early stage was observed in 69 (95%) and 57 (60%) endometrial and ovarian cancers, respectively. Of 72 cases, 37 had pretreatment measurement of CA125, with a median of 377.8 IU/ml (range: 15-5,135). CA125 values were all over 35 IU/ml, except for two. Regarding pathologic characteristics, endometrioid tumor type was found in 69 (95.8%) and 53 (73.6%) endometrial and ovarian carcinomas. Fifty-four cases (75%) of these two distinct cancers had exactly the same cell type. Forty well-differentiated endometrial tumors and 31 well-differentiated ovarian tumors were found in 66 specimens. Lymphovascular space invasion was detected in only one-tenth of cases. In 34 of 66 pair malignancies, precancerous lesions were found in at least one cancer, with precancerous lesions found in both cancers in 7 cases. Deep myometrial invasion was identified in 10 of 72 cases (13.9%) of endometrial cancer (Table 2).

Complete response after primary treatment was 97.2% in endometrial cancer and 97.3% in ovarian cancer. Accordingly, progression of disease was observed in 2.8% of endometrial cancer and in 2.7% of ovarian cancer. Two patients succumbed to their disease. Recurrence was identified in 2 endometrial and 6 ovarian cancer patients. The 5-year OS was 98.1% (95% CI: 94.6-100), 98.1% (95% CI: 94.6-100), and 98.3% (95% CI: 95-100) for paired cancer, endometrial cancer, and ovarian cancer, respectively. The 5-year recurrence-free survival (RFS) was 86% (95% CI: 76.2-95.8), 96.8% (95% CI: 92.5-100), and 89% (95% CI: 79.8-98.2) for paired cancer, endometrial cancer, and ovarian cancer, respectively. In univariate and multivariate analysis for prognostic factors associated with OS, no significant association was found for menopausal status, presence of endometrioid tumor at both sites, residual tumor, depth of myometrial invasion, grade of endometrial cancer, or grade and stage of ovarian cancer. In contrast, residual tumor and depth of myometrial invasion were identified as independent prognostic factors related to RFS. More specifically, patients with residual tumor >0 to ≤1 cm and >1 cm had increased risk of recurrence (HR: 6.7 and 22.6, respectively) compared with those without residual tumor. Similarly, the recurrence rate was greater if deep myometrial invasion was present (HR: 11.6) (Table 3).

Gynecologic cancer coexisting with non-gynecologic cancer (GNC)

In contrast to the very low proportion in the MPGC group, the majority of cases in the GNC group were metachronous cancers (90.4%). The most common type of coexisting non-gynecologic tumor was breast cancer (41/52). In a majority of those cases, breast cancer was found before the discovery of gynecologic cancer. The mean interval between diagnosis of the two distinct malignancies was 5.6 years for breast-endometrial cancer, and 8 years for breast-ovarian cancer. Mean age at diagnosis of breast cancer was 54.8 years. Ductal carcinoma accounted for 97.8% (40/41) of all histologies. Moderately differentiated carcinoma was found in three-fifths of cases, while 30% were poorly differentiated. Precancerous lesion was detected in approximately 25% of breast cancer patients. The most frequently observed ovarian histologic cell type associated with breast cancer was serous cell type (8/16), followed by clear cell (5/16) and endometrioid (3/16). In contrast, endometrioid was the most prevalent pathology found in endometrial cancer coexisting with breast cancer. Concerning 36 cases with available hormone profiles, 75.6% and 61.0% of breast cancer patients had positive estrogen receptor and positive progesterone receptor, respectively. Thirty-six percent of women were HER2-negative, and 14.0% were HER2-positive. The remaining proportion of patients had borderline result

TABLE 1. Patient characteristics and oncologic outcomes compared between MPGC and GNC

Variables	MPGC (n=94)		GNC (n=52)		*P*-value
Synchronous cancer, n (%)	86 (91.5%)		5 (9.6%)		***<0.05***
Interval between 1st and 2nd cancers (months), median (range)	0 (0-290)		63 (1-147)		***<0.05***
Paired cancer sites, n (%)	Endometrium-ovary	72 (76.6%)	Endometrium-breast	19 (36.5%)	N/A
	Cervix-ovary	10 (10.6%)	Ovary-breast	19 (36.5%)	
	Cervix-endometrium	5 (5.3%)	Endometrium-colon	4 (7.7%)	
	Others	7 (7.4%)	Others	14 (22.9%)	
Age at diagnosis of first malignancy (years), mean±SD	52.7±10.5		54.5±10.51		0.371
Age at diagnosis of EC (years), mean±SD	53.4±10.4		62.5±8.5		0.454
Age at diagnosis of OC (years), mean±SD	53.2±10.0		55.9±11.1		0.251
Age at diagnosis of CC (years), mean±SD	50.7±9.3		N/A		N/A
Age at diagnosis of BC (years), mean±SD	N/A		54.8±9.9		N/A
Nulliparous, n (%)	53 (56.3%)		18 (34.6%)		***0.038***
Menopause, n (%)	46 (48.9%)		40 (76.9%)		***0.006***
Obtained family history of malignancy, n (%)					
Yes	19 (20.2%)		35 (67.3%)		***<0.05***
Positive	8 (8.5%)		15 (28.8%)		
Negative	11 (11.7%)		20 (38.5%)		
No	75 (79.8%)		17 (32.7%)		
Offered genetic testing, n (%)					
Performed	2 (2.1%)		15 (28.8%)		N/A
HNPPC	2 (2.1%)		4 (7.7%)		
BRCA1 mutation	0 (0.0%)		4 (7.7%)		
BRCA2 mutation	0 (0.0%)		1 (1.9%)		
Negative result	0 (0.0%)		4 (7.7%)		
Deny testing	0 (0.0%)		2 (3.8%)		
VTE, n (%)	6 (6.4%)		5 (13.2%)		0.296
Stage of EC, n (%)					
I-II	73 (93.6%)		15 (55.6%)		***<0.05***
III-IV	5 (6.4%)		12 (45.4%)		
Stage of OC, n (%)					
I-II	66 (80.5%)		8 (38.0%)		***<0.05***
III-IV	16 (19.5%)		13 (62.0%)		
Stage of BC, n (%)					
I-II	N/A		27 (65.9%)		N/A
III-IV			14 (34.1%)		
CR, n (%)	85 (92.4%)		37 (71.1%)		***<0.05***
Recurrence, n (%)	15 (16.0%)		25 (48.1%)		***<0.05***
Death, n (%)	4 (4.2%)		5 (9.6%)		***<0.05***
5-year OS, (%)	96.1%		97.6%		0.77
5-year RFS, (%)	87.3%		79.6%		***0.036***

A *p*-value<0.05 indicates statistical significance

Abbreviations: MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer; N/A, not applicable; SD, standard deviation; EC, endometrial cancer; OC ovarian cancer; CC, cervical cancer; BC, breast cancer; HNPCC, hereditary nonpolyposis colorectal cancer; BRCA, breast cancer gene; VTE, venous thromboembolism; CR, complete response; OS, overall survival; RFS, recurrence-free survival

TABLE 2. Pathologic characteristics of synchronous endometrial and ovarian cancers (n=72).

		Ovarian cancer, n			
Endometrial cancer, n	FIGO staging	I	II	III	IV
	I	37	15	13	2
	II	2	0	0	0
	III	2	0	0	0
	IV	1	0	0	0
	Histology	Endometrioid	Serous	Clear cell	Others
	Endometrioid	52	2	4	11
	Serous	0	2	0	
	Clear cell	1	0	0	
	Grading	Grade 1	Grade 2	Grade 3	
	Grade 1	25	10	5	
	Grade 2	4	10	6	
	Grade 3	2	2	2	
	LVSI	Presence	Absence		
	Presence	0	6		
	Absence	1	54		
	Precancerous lesion	Presence	Absence		
	Presence	7	6		
	Absence	21	32		
	Myometrial invasion				
	No myometrial invasion	30			
	Superficial myometrial invasion	32			
	Deep myometrial invasion	10			

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion

TABLE 3. Univariate and multivariate analysis for factors significantly associated with recurrence-free survival in patients diagnosed with synchronous endometrial and ovarian cancers (n=72).

Variables	Univariate			Multivariate		
	HR	*P*-value	95% CI	HR	*P*-value	95% CI
Menopausal status						
Premenopause	1					
Menopause	1.65	.512	.37-7.38			
Histologic cell type						
Both endometrioid	1					
Others	2.11	.308	.5-8.86			
Residual tumor						
None	1			1		
>0 - ≤1 cm	3.44	.13	.69-17.1	6.65	***.036***	1.13-38.99
>1 cm	8.28	***.021***	1.38-49.59	22.58	***.005***	2.55-199.73
Grade of EC						
1	1					
2-3	2.32	.249	.56-9.72			
Grade of OC						
1	1					
2-3	1.004	.996	.25-4.03			
Stage of OC						
I-II	1					
III-IV	1.92	.43	.39-9.52			
Myometrial invasion						
Inner half	1			1		
Outer half	4.24	***.048***	1.01-17.76	11.58	***.007***	1.94-69.19

A *p*-value<0.05 indicates statistical significance

Abbreviations: HR, hazard ratio; CI, confidence interval; EC, endometrial cancer; OC ovarian cancer

(a score of 2+). Of the 19 breast-endometrial cancer patients, 17 had taken tamoxifen. Mean duration of tamoxifen use was 4.5 years. Median duration between start of tamoxifen treatment and endometrial cancer diagnosis was 5.3 years (range: 1.9-13.3). Five-year OS and 5-year RFS were 97.3% (95% CI: 92-100) and 94.3% (95% CI: 86.5-100) for breast cancer (Table 1).

In the GNC group, the 5-year OS and 5-year RFS was 97.6% (95% CI: 92.9-100) and 79.6% (95% CI: 68.2-91), respectively (Table 1). There was no significant difference between MPGC and GNC for 5-year OS (p=0.77). In contrast, the 5-year RFS was significantly longer among MPGC than and among GNC (p=0.036) (Fig 1). Among patients with endometrial cancer, in which advanced stage was presented in nearly half of all cases, the 5-year OS and 5-year RFS was 78.6% (95% CI: 59.2-98) and 71.1% (95% CI: 50.9-91.3), respectively. For patients with ovarian cancer, the 5-year OS and 5-year RFS were 92.3% (95% CI: 77.8-100) and 33.5% (95% CI: 9.4-57.6), respectively. Sixty-two percent of ovarian cancer patients presented at late stage.

Family history of cancer and genetic testing

More GNC patients than MPGC patients were concerned about having hereditary cancer syndrome. Almost three times as many GNC patients as MPGC patients were assessed for family history of cancer. Subsequently, fewer MPGC patients (2.1%) than GNC patients (28.8%) were offered genetic testing. This study revealed 11 positive tests, as follows: 6 hereditary nonpolyposis colorectal cancer (HNPCC), 4 BRCA1 mutation, and 1 BRCA2 mutation. The detailed results of genetic testing in those 11 patients is shown in Table 4.

DISCUSSION

This study focused on multiple primary malignancies in gynecologic cancer patients in two aspects: multiple primary gynecologic cancers (MPGC) and gynecologic cancer coexisting with non-gynecologic cancer (GNC). With regard to clinical characteristics, there was no significant difference in age at diagnosis in patients with paired cancer, endometrial cancer and ovarian cancer between the MPGC group and the GNC group, although endometrial cancer was detected at older age in the GNC group (62.5 vs. 53.4 years). This was concordant with our finding that significantly more GNC women than MPGC women were postmenopausal. Furthermore, less GNC patients than MPGC patients were identified at early stage of endometrial and ovarian cancers. This finding may be explained by accidental detection of asymptomatic second gynecologic malignancy during surgical staging of primary gynecologic cancer, which normally involves resection of the uterus and both adnexa, resulting in diagnosis of secondary tumor at an earlier stage. As a result, MPGC patients had better oncologic outcomes than GNC patients relative to complete response rate and recurrence-free survival.

Concerning synchronous endometrial and ovarian cancers, the prevalence rates observed in this study were comparable with those reported in prior studies, including 1-2% of gynecologic cancer, 3-5% of endometrial cancer, and 10% of ovarian cancer.[12-14] Several retrospective studies evaluated the clinical characteristics and oncologic outcomes of synchronous endometrial and ovarian cancers, as shown in Table 5. Mean age at diagnosis was lower in MPMT (mean age of 53 year) than in those with single primary cancer. This was consistent

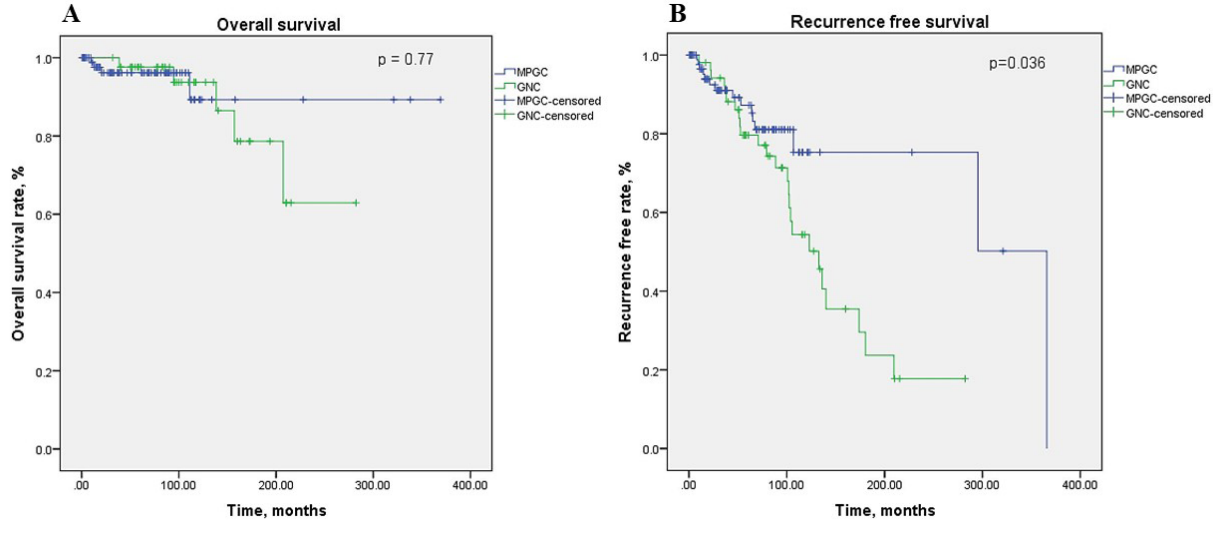


Fig 1. Kaplan-Meier survival analysis with data comparisons by log-rank test. A) Comparison of overall survival between the MPGC and GNC groups (5-year overall survival: 96.1% vs. 97.6%, respectively; p=0.77). B) Comparison of recurrence-free survival between the MPGC and GNC groups (5-year recurrence-free survival: 87.3% vs. 79.6%, respectively; p=0.036).
Abbreviations: MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer

TABLE 4. Multiple primary malignancies in gynecologic patients with positive genetic testing (n=11)

Genetic test result	FHC	Group	First cancer, age at diagnosis (yr)	Stage	Recurrence, RFS (mo)	Status, Time to survival (mo)	Second cancer, age at diagnosis (yr)	Stage	Recurrence, RFS (mo)	Status, time to survival (mo)
HNPCC	Yes	MPGC	Endometrium, 33	I	No	Remission, 38	Ovary, 38	II	No	Remission, 38
HNPCC	Yes	MPGC	Endometrium, 33	II	No	Remission, 18	Ovary, 38	I	No	Remission, 18
HNPCC	Yes	GNC	Colon, 63	II	No	Remission, 58	Endometrium, 64	I	No	Remission, 46
HNPCC	Yes	GNC	Colon, 70	I	No	Lost to FU, 52	Endometrium, 74	IV	Yes, 47	Loss FU, 11
HNPCC	Yes	GNC	Breast, 44	II, ER+, PR+, HER2-	No	Remission, 51	Endometrium, 44	III	No	Remission, 46
HNPCC	Yes	GNC	Ovary, 45	II	Yes, 132	Remission, 135	Breast, 51	I, ER+, PR+, HER2-	No	Remission, 64
BRCA1	Yes	GNC	Breast, 35	II, ER-, PR-, HER2 equivocal	No	Lost to FU, 193	Ovary, 49	IV	Yes, 12	Lost to FU, 31
BRCA1	Yes	GNC	Breast, 43	III, ER+, PR+, HER2-	Yes, 100	Remission, 140	Ovary, 50	I	No	Remission, 55
BRCA1	Yes	GNC	Ovary, 46	III	Yes, 22	Remission, 60	Breast, 51	III, ER+, PR, HER2 equivocal	No	Remission, 5
BRCA1	No	GNC	Ovary, 60	I	No	Remission, 50	Breast, 60	I, ER-, PR-, HER2 equivocal	No	Remission, 49
BRCA2	No	GNC	Breast, 60	I, ER+, PR+, HER2-	No	Remission, 37	Ovary, 65	IV	Yes, 18	Stable disease, 90

Abbreviations: FHC, family history of cancer; mo, months; RFS, recurrence-free survival; MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer; HNPCC, hereditary nonpolyposis colorectal cancer; BRCA, breast cancer gene; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; FU, follow-up

with the findings of a German study that compared clinical characteristics of synchronous cancer to matched controls with either endometrial or ovarian cancer without other malignancies.[15] More than half of patients had premenopausal status, especially if endometriod cell type was present in both organs. Although our study did not include information about body mass index (BMI), data from a previous study showed overweight in all non-Asian populations and in the study of Chiang, *et al.*[16] Since younger age, premenopausal status, overweight, and endometriod cell type were predominant in coexisting endometrial and ovarian cancers, hormonal effect is a possible causative factor in the development of MPMT. Concerning pathologic characteristics, our results were consistent with the pathologic criteria of synchronous cancer proposed by Scully, *et al.*[17], including common

TABLE 5. Literature review of studies in synchronous endometrial and ovarian cancers

Authors, country, year	N	Age (yr)	P0 (%)	Menopause (%)	BMI (kg/m²)	EM in both sites (%)	Endometrial cancer			Ovarian cancer				5-yr RFS (%)	5-yr OS (%)	Prognostic factors
							Stage I-II (%)	G1 (%)	Deep MI (%)	EH (%)	Stage I-II (%)	G1 (%)	ES (%)			
Eifel, USA, 1982[1]	16	41	50	37		55.1			6						100	Both EM
	EM-EM															
	11 others	61	18	90					63						45	
Soliman, USA, 2005[2]	84	50	33	49	28	67.9	92	42	18			37				Both EM
	all															
	57 EM-EM	**50**	33	**43**	28										**OS 119 mo**	
	10	**63**	40	75	27										**OS 48 mo**	
	EM -serous															
	7	54	50	67	27											
	EM-clear cell															
Oranratanaphan, Thailand, 2008[3]	14	47	93	7.1	22.5		100		0		85.7			64.2	92.8	
Chiang, Taiwan, 2008[4]	27	47	33	37	26.5		96	64			80	62			85	Early stage of EC and OC
Caldarella, Italy, 2008[5]	46	55				45.6		46	26	4.3		35			67.5	Age ≤50, grade 1 at both sites, but not EM at both sites
Williams, USA, 2009[6]	1,355	54.7					72.5	43			47.9	28			79	
Gungor, Turkey, 2009[7]	11	58.3	9	72.7	29.4	0	100	73			100	45				
Lim,Singapore, 2011[8]	46	47.3					82.5	70	13		80.5	48			84	Age (borderline significance)
Rodolakis, Greece, 2012[9]	30	51	37	47		60	93	43	17	47	76	17	27	84.2	84.2	Not histologic cell type
Alhilli, USA, 2012[10]	15	55.1	33		31.2	66	100	73			100	47	33.3			
Broeders, Netherlands, 2012[11]	21	56.2	47	70			76.2				76.2		19		80	
*Song, Korea, 2013[12]	21	33	81	0	22.9	42.8	76	52	24		62	38				
	(age <40 yr)															
Song, Korea, 2014[13]	123	50.4	38	56.1	24.1	45.5	71.5	43	29.3		66.7	29		66.9	80	Pretreatment CA125, stage of OC
Heitz, Germany, 2014[14]	77	55.8	26			48.1	94.8				68.8		24.6	76.3	71.6	
Kobayashi, Japan, 2015[15]	32	all	49.2	53.1	43.8	22.8	75	93.8	81		75	62				
	24	**46.3**	58.3	**29.2**	22.2								**87.5**			
	EM-EM															
	8	**58.5**	37.5	**87.5**	24.6								**37.5**			
	others															
Bese, Turkey, 2016[16]	31	**52.6**	45.2			93.6	26	16.1	22.6	41.9					67.7	Residual tumor
Present study, Thailand, 2018	72	53.3	70.8	**48.4**		72	95	61	13.9	19.6	60	47	42.4	86	98.1	Residual tumor, myometrial invasion

Statistically significant values are in bold, *Includes only women aged less than 40 years

Abbreviations: P0, nulliparity; BMI, body mass index; EM, endometrioid; G, grade; MI, myometrial invasion; EH, endometrial hyperplasia; ES, endometriosis; RFS, recurrence free survival; OS, overall survival; EC, endometrial cancer; OC, ovarian cancer

well-differentiated grade, low frequency of vascular space invasion, and deep myometrial invasion. Broeders, *et al.* reported that deep myometrial invasion was detected in 28.6% of synchronous endometrial ovarian cancer, 100% of endometrial cancer with ovarian metastasis, and 76.5% of ovarian cancer with endometrial metastasis[18]. Several previous series and the present study all found histologic similarity in paired tumors. Accordingly, some suggest the potential value of immunohistochemistry and molecular studies, such as loss of heterozygosity on chromosome, DNA flow cytometry, beta-catenin, microsatellite instability, and PTEN.[14,19] That acknowledged, the efficacy of molecular study in this setting has not yet been established, and no consensus has yet been reached regarding diagnostic criteria. Regarding oncologic outcomes, the overall survival rate in this study was substantially higher than in other studies, but our rate was comparable to the rate reported by Oranratanaphan, *et al.*, who also reported from Thailand.[20] Many previous studies reported that synchronous cancer had better prognosis than single primary cancer. For example, our study reported 5-year survival rates of 98.1% and 98.3% for endometrial and ovarian cancer in paired malignancy, while another Thai study reported 5-year survival rates of 89% and 69.3% for endometrial and ovarian cancer in patients with single malignancy.[21] This may be due to more favorable characteristics found in synchronous cancer. In contrast, studies from Germany and the Netherlands showed similarity in overall survival rate between single and paired tumor, even after matching for potential factors, such as age, stage, and ECOG score.[15,18] Our study identified residual tumor and myometrial invasion as independent prognostic factors associated with shorter recurrence-free survival. A previous study from Turkey also found residual tumor to be a factor significantly associated with RFS.[14] Eifel, *et al.*, and Soliman, *et al.*, found presence of endometrioid cell type at both sites to be associated with better prognosis.[22,23] However, that finding was not consistent with the finding of two European studies.[24,25] Specifically, Caldarella, *et al.*, and Rodolakis, *et al.*, found age ≤50 years to be the only statistically significant predictor of RFS. Data from Taiwan and Korea revealed stage of ovarian cancer to be an important factor. It should be noted that relevant prognostic factors varied among articles.[13,16]

Regarding our analysis of GNC, breast cancer was found to be the most common coexisting non-gynecologic tumor. In most cases, breast cancer presented first, followed by the gynecologic malignancy. This finding was identical to that reported by Liou, *et al.*, and Martin-Dunlap, *et al.*,[26,27] but contrasted with the reported finding of Grzankowski, *et al.*[28] In support of the causal relationship between tamoxifen use and the development of endometrial cancer, 14 of 17 cases in this study developed endometrial cancer after starting tamoxifen. The mean interval between diagnosis of the two distinct carcinomas was 5.6 years. Previous studies reported intervals that ranged from 3-10 years.[21,27, 28] For this reason, long-term surveillance should be encouraged since secondary cancer can develop as long as a decade after the initial cancer diagnosis. Regarding coexisting breast and ovarian cancer in this study, the most frequently observed ovarian histologic cell type was serous. Correspondingly, Liou, *et al.*, reported that serous ovarian carcinoma was associated with breast cancer, but that endometrioid cell type was not.[26]

The main limitation of the current study was its retrospective design, which made it vulnerable to potential biases due to missing data. In addition, the lack of pathologic review by the same set of reviewers could raise concerns about interobserver variability. The strength of this study is that 10 years of data from Thailand's largest national tertiary referral center were included and analyzed between MPGC and GNC. In addition, the authors performed and included a literature review of studies in synchronous endometrial and ovarian cancers – the most common paired cancer found in this study.

CONCLUSION

Prevalence of MPGC in this study was 1.2%. Five-year recurrence-free survival was significantly longer among MPGC than among GNC. Three-quarters of MPGC patients had synchronous endometrial-ovarian cancer. Residual tumor and depth of myometrial invasion were identified as prognostic factors independently associated with recurrence-free survival in patients with synchronous endometrial-ovarian cancer.

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The Psychometric Property of the Short Thai Version of the Philadelphia Mindfulness Scale

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ABSTRACT

Objective: To develop and investigate the psychometric property of the short Thai version of the Philadelphia Mindfulness Scale (PHLMS).

Methods: The pooled data from the mindfulness invention studies between 2011 and 2014 were analyzed. The items of original version were selected by 3 methods i.e., mean difference between the two groups of high score and low score by t35-test, researchers' opinion and corrected item total correlation. Two forms of short Thai version were developed. These forms were analyzed by using exploratory factor analysis (EFA) in randomly selected 303 cases and only the selected form was confirmed by confirmatory factor analysis (CFA) in 873 cases by using the Mplus program. The goodness of fit indices was determined by Chi-square index, root mean square error of approximation (RMSEA), comparative fit index (CFI) and Tucker Lewis Index (TLI). Pearson's correlation was used to analyze the discriminant validity with Hospital Anxiety Depression Scale (HAD).

Results: Only the researchers' opinion version (ROV) containing 10 items was confirmed by CFA and had factor loadings between 0.50-0.80. The goodness of fit was acceptable. The ROV and each domain (awareness and acceptance) had acceptable composite reliability at 0.86, 0.72 and 0.83 respectively.

Conclusion: The short version of PHLMS contained 10 items and demonstrated the good validity among clinical cases, beginners in meditation practice and care givers; and could classify people with different frequencies of meditation practice.

Keywords: Philadelphia Mindfulness Scale; psychometric; Thai version (Siriraj Med J 2018;70: 320-326)

INTRODUCTION

Since mindfulness based stress reduction (MBSR) programs have been developed by Kabat Zinn in 1985[1], the benefit outcomes have been established by clinical outcomes and self-rating scales. The mindfulness assessment scales have followed the mindfulness operation definition by Bishop et al which consisted of two major components i.e., self-regulation of attention and orientation to experience.[2] The assessment scales are self-rating reporting and contain 1 to 5 domains which range from 10 to 39 items.[3] Some scales have been popular to use across cultures such as Mindful Attention Awareness Scale (MAAS)[4,5], Kentucky Inventory of Mindfulness Scale (KIMS)[4] and Philadelphia Mindfulness Scale (PHLMS).[6]

Christopher et al reported that culture and race had impacted on the structure domain of the mindfulness questionnaires (KIMS) among Thai and US students[4] and also Thai monks and US students.[7] KIMS had some items which crossed domains and did not follow the original version which might be from concept of mindfulness practice or local culture.[7] Therefore users should be aware of cross cultural effects before applying the tool to evaluate the outcome of mindfulness program.

The Philadelphia Mindfulness Scale (PHLMS), followed the concept proposed by Bishop et al, and contains 2 components which are awareness and acceptance. It has been translated into various languages such as Lebanese[8], Spanish[9], Chinese[10] and Thai.[11] The Thai version was tested among hospital personnel and confirmed that 19 items (except item number 7) followed the original version.[11]

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It could be explained by a few cases (103 cases) and most were female (84.5%). However, the internal consistency demonstrated by Cronbach's alpha was high (0.87 and 0.88 for awareness and acceptance respectively).

The Thai PHLMS version has been used as a concurrent validity study of the Sati Assessment Scale[12] and in research studies.[13,14] From our experiences, the 20 item-PHLMS was too long for clinical practice especially in patients with uneducated or low educated level. The short 10–item Chinese PHLMS version was selected by factor loadings (above 0.30) and Goenka's concept of vipassana and had indices of goodness better than that of the full version. However, this short version had been conducted via online social media in 200 Buddhists, of whom (102 persons) were mainly general followers of Buddhism or secular. The Spanish and Lebanese did not adjust the questionnaire. Therefore, this study was aimed to develop the short version and to explore psychometric properties in variety of samples such as care givers, clinical cases, and beginner in meditation practice in order to apply the short version in general practice.

MATERIALS AND METHODS

Secondary data from the Sati assessment scale[12,15] were selected that is; age, sex, meditation practice, PHLMS, and Hospital Anxiety Depression Scale (HAD). This study was approved by Srithanya Ethical committee (Q 9/2557) on 19 September 2014.

The full PHLMS version is a rating scale (1-5; never to very often) which consists of 20 items divided into 2 domains i.e., the odd number items for awareness domain and the even numbers for acceptance domain. Volunteers had to rate the questionnaire by her/himself within 1 week.

The HAD[16] is a rating scale (0-3; always to never) consisted of 14 items and was divided into 2 parts i.e. the odd numbers for anxiety (HAD_anx) and the even numbers for depression (HAD_dep).

Methods

The first step was item selection by 3 different ways as follows:

i. Corrected item-total correlation (CITC) is one of the best efficacies of item selection.[17]

ii. Mean difference of each item between groups: Each item of PHLMS was classified into the group of high score and that of lower score by percentile 35 (t_{35} -test)[18] to ensure adequate number of selected cases. Only significant items were selected.

iii. Item selection by researchers' opinion regarding the definition of Sati by the Tripitaka and the Satipatthana Sutta.[19]

The second step was psychometric property study by exploratory factor analysis and confirmatory factor analysis. The derived items were further analyzed for internal consistency by Cronbach's alpha and composite reliability and the discriminant validity by Hospital Anxiety Depression scale (HAD). Levels of mindfulness and practice were related to stress and psychological symptoms.[20]

The sample was divided into 2 groups by the SPSS command: 'data/select cases/ random samples of case/ sample size/ approximately/25% of all cases' in order to identify the possible model by exploratory factor analysis (EFA) in the group one and confirmatory factor analysis (CFA) in the other group by the Mplus program.

Statistical analysis

Descriptive analysis was used to compare the demographic data by Chi-square and t-test between two groups of samples.

According to the original version, two factors were specified and related in EFA, and promax rotation, polychoric correlation and weighted least squares (WLS) methods of analysis were applied. The factor loading should be at or above 0.3 and root mean square of residual (RMSR) was less than 0.05.[21]

The confirmatory factor analysis (CFA) was analyzed in the second group of samples. The goodness of fit indices in this study were comparative fit index (CFI) and Tucker Lewis Index (TLI; >0.95) and root mean square error of approximation (RMSEA; <0.08).[22,23]

Internal consistency by Cronbach's alpha and composite reliability[24] of the short version were calculated. The mean score of derived items was correlated to that of the Hospital Anxiety Depression Scale by Pearson's correlation coefficient.

RESULTS

Total sample was 1,176 cases. Of these, 355 were psychiatric care-givers, 286 participants at Yong Buddhist Association of Thailand, 259 health personnel, 175 university students and 101 medical cases. Most were female (70.7%) and average age at 40.1 (SD=15.0) years, single (58%) primary to secondary education level (44.6%). There were 833 persons experienced in formed meditation, but only 99 person (11.9%) practiced regularly. The first group (303 persons) and the other (873 persons) did not have statistical difference of age, sex education, meditation practice and mean scores of two domains of the PHLMS as shown in Table 1.

TABLE 1. Demographic data of 2 groups

Variables		N (%)			
		Group 1 (N= 303)	Group 2 (N=873)	Total	*P*-value
Sex	Male	77 (25.3)	268 (30.7)	345 (29.4)	0.08
	Female	225 (74.7)	604 (69.3)	829 (70.6)	
Average age (SD)		40.4 (14.7)	40.0 (15.2)	40.1 (15.0)	0.20
Age range		17-83	18-79	17-83	
Marital	Single	169 (56.0)	520 (59.8)	689 (58.8)	0.35
	Married	77 (25.5)	217 (25.0)	294 (25.1)	
	Separated	56 (18.5)	132 (15.2)	188 (16.1)	
Education	≤Secondary	114 (37.6)	332 (38.2)	446 (38.0)	0.64
	Bachelor	89 (29.4)	274 (31.5)	363 (31.0)	
	≥Master	100 (32.8)	263 (30.3)	363 (31.0)	
Meditation					
	Rarely	129 (60.1)	367 (58.1)	496 (59.5)	0.82
	Sometimes	35 (15.9)	97 (15.8)	132 (15.8)	
	Frequently/Always	58 (26.1)	147 (24.1)	205 (24.6)	
Duration	<20 Min	134 (61.2)	391 (64.6)	536 (63.7)	0.57
	20-30 Min	56 (25.6)	147 (24.4)	207 (24.6)	
	>30 Min	29 (13.2)	66 (10.9)	98 (11.7)	
Sum Awareness Score		33.9 (5.7)	34.4 (6.0)	34.2 (6.0)	0.20
Sum Acceptance Score		29.9 (6.5)	29.4 (7.0)	29.5 (6.9)	0.28

Item selection results

According to CITC values, the sequence of items were 16, 13, 10, 14, 12, 20, 11, 17, 15 and 19 respectively. For the mean difference between groups by t_{35}, no item was excluded. (Table 2). Therefore, there were only two short forms; that is "c" (from CITC) and "r" (r= researcher's opinion) in order to explore by EFA.

EFA

EFA was done in the first group, but the full version of PHLMS was a bi-factor model as original version and the fit indices were not acceptable. (χ^2 =1002.2, df =151, RMSR =0.115) The short form "c" (SFC) had two domains and did not have acceptable fit indices either. (χ^2 =400.1, df =26, RMSR =0.099) The short form "r" (SFR) comprised 2 domains of 5 items which showed acceptable fit indices. (χ^2 =142.1, df =26, RMSR =0.05) and factor loading weights were ranged 0.32 – 0.84. The SFR was further analyzed by CFA.

CFA

CFA was studied in the second group. The full original version in which the odds number items for awareness domain and the even number items for acceptance domain (model_A), had fit indices which were not acceptable. The SFR was divided into 2 domains; that is item number 1, 5, 9, 11 17 and 19 were in awareness domain and item numbers 14, 16, 18 and 20 were in acceptance domain. The error between item 5-9 and item18 - 20 were adjusted (model_B) and factor loading weights ranged 0.52 – 0.84. Each item explained common variance of mindfulness scale from 27 to 71% and the fit indices were acceptable. Then second order confirmatory analysis was calculated in order to confirm the SFR which explained the mindfulness scale (model_C). The fit indices were not different from those of model_B. (Table 3) The factor loading weights of the awareness domain and acceptance were 0.90 and 0.56 respectively.

TABLE 2. Item selection by CITC, t_{35}, researchers' opinion (res)

PHLMS	CITC	p(t_{35})	res
1. I am aware of what thought passing through my mind.	0.38	<0.01	✓
2. I try to distract myself when I feel unpleasant emotions.	0.39	<0.01	
3. When talking with other people. I am aware of their facial and body expressions.	0.34	<0.01	
4. There are aspects of myself I don't want to think about.	0.38	<0.01	
5. When I shower I am aware of how the water is running over my body.	0.30	<0.01	✓
6. I try to stay busy to keep thoughts and feelings from coming to my mind.	0.23	<0.01	
7. When I am startled, I notice what is going on inside my body.	0.42	<0.01	
8. I wish I could control my emotions more easily.	0.40	<0.01	
9. When I walk outside, I am aware of smells or how the air feels against my face.	0.34	<0.01	✓
10. I tell myself that I shouldn't feel sad.	0.47	<0.01	
11. When someone asks how I am feeling, I can identify my emotions easily.	0.43	<0.01	✓
12. There are things I try not to think about.	0.46	<0.01	
13. I am aware of thoughts I'm having when my mood changes.	0.50	<0.01	
14. I tell myself that I shouldn't feel sad.	0.47	<0.01	✓
15. I notice changes inside my body, like my heart beating faster or my muscles getting tense.	0.36	<0.01	
16. If there is something I don't want to think about, I'll try many things to get it out of my mind.	0.50	<0.01	✓
17. Whenever my emotions change, I am conscious of them immediately.	0.42	<0.01	✓
18. I try to put my problems out of mind.	0.39	<0.01	✓
19. When talking with other people, I am aware of the emotions I am experiencing.	0.42	<0.01	✓
20. When I have a bad memory, I try to distract myself to make it go away.	0.44	<0.01	✓

Abbreviations: p(t_{35}) = p-value from t-test, res = researhcers'opinion

TABLE 3. Factor loadings and variances (R^2) (N=870)

	Model_B				Model_C			
Factor	**Loading**	**SE**	**P-value**	**R^2**	**Loading**	**SE**	**P-value**	**R^2**
Aware								
item 1	0.50	0.03	<0.01	0.25	0.50	0.03	<0.01	0.27
item 5	0.53	0.03	<0.01	0.28	0.53	0.03	<0.01	0.28
item 9	0.56	0.03	<0.01	0.31	0.56	0.03	<0.01	0.31
item 11	0.62	0.02	<0.01	0.38	0.62	0.02	<0.01	0.38
item 17	0.80	0.02	<0.01	0.63	0.80	0.02	<0.01	0.63
item 19	0.65	0.02		0.42	0.65	0.02	<0.01	0.42
Acceptance								
item 14	0.70	0.02	<0.01	0.50	0.70	0.02	<0.01	0.49
item 16	0.79	0.02	<0.01	0.62	0.79	0.02	<0.01	0.58
item 18	0.80	0.02	<0.01	0.64	0.80	0.02	<0.01	0.71
item 20	0.73	0.02	<0.01	0.54	0.73	0.02	<0.01	0.60
	PCC							
Accept with aware	0.52	0.03	<0.01	mindful by				
5 - 9	0.30	0.04	<0.01	aware	0.90	.01	<0.01	
18 - 20	0.24	0.05	<0.01	accept	0.58	.03	<0.01	
					PCC	SE		
				5 - 9	0.30	0.04	<0.01	
				18 - 20	0.24	0.05	<0.01	

Abbreviations: SE = estimate standard error, PCC= polychoric correlation coefficient

Reliability study

Cronbach's alpha values for the whole 10 items, awareness and acceptance domain were 0.81, 0.75 and 0.82 respectively in the second group. The corrected item-total correlations (CITC) were between 0.35 - 0.59. The composite reliability of the whole short form, awareness and acceptance domains of model_C by the equation 5 of Raykov[24] were 0.86, 0.72 and 0.83 respectively.

Discriminant validity study

The discriminant validity was tested in 765 persons consisting of 355 psychiatric care-givers, 160 health personnel, 149 participants at Yong Buddhist Association of Thailand and 101 medical cases. Pearson's correlation coefficient between awareness and acceptance domains and HAD_anx were -0.14, -0.17 ($p<0.01$) respectively and those of HAD_dep were -0.25, -0.32 ($p<0.01$) respectively.

Discriminant power study

In the mean scores among different experiences of meditation, the PHLMS of awareness were significantly different between each group. For the acceptance domain only the frequently/always practice was significantly different from the others. (Table 5)

TABLE 4. Model fit indices (N=870)

Model	χ^2/df	RMSEA	CFI	TLI
Model_A 20 items	2,304.9/169	0.121(0.116,0.125)	0797	0.772
Model_B (short "r")	130.0/32	0.059(0.049, 0.070)	0.982	0.975
Model_C	130.0/32	0.059(0.049, 0.070)	0.982	0.975

Abbreviations: χ^2= chi square, df= degree of freedom, RMSEA = root mean square error of approximation, CFI = comparative fit index, TLI= Tucker Lewis Index

TABLE 5. Comparing mean scores of PHLMS meditation practice (N=833)

	Awareness			Acceptance		
Meditation practice	Mean (SD)	95% CI	P-value	Mean (SD)	95% CI	P-value
Rarely	20.9(3.5)**	20.6, 21.3	<0.01	11.2(3.5)*	10.9, 11.5	0.02
Sometimes	21.1(4.1)**	20.4, 21.8		11.5(3.5)+	10.8, 12.1	
Frequently/Always	22.3(3.7)**	21.8, 22.8		10.5(3.7)*+	10.0, 11.0	
average	21.3(3.7)	21.1, 21.6		11.1(3.6)	10.8, 11.3	

*, + between group and p= 0.04 and ** p<0.01

DISCUSSION

Item selection by statistical method yielded some drawbacks due to data distribution, and diversity of study sample.[7] Culture and beliefs also impacted on concept of item development[6] which considered some acceptance items were avoidance instead of acceptance.[3]

Some items of the short form in this study differed from Chinese version[10] even though they follow Buddhism which might be explained by culture and beliefs. We considered the item 3 was related to external person like Zeng and et al. The item 7 was related to the item 11 and also the item 13 and the item 1, therefore we selected the items (1, 11) which had wider point of view. Finally selected items contained both negative and positive aspects which followed the psychological questionnaire development.[25]

Error was adjusted between the item number 5-9 (body awareness) and the number 18-20 (mind) according to the Satipatthana Sutta. Therefore model modifications for these correlations were possible as the awareness of the first pair and the acceptance for the other pairs.

The two domains of SFR followed the original

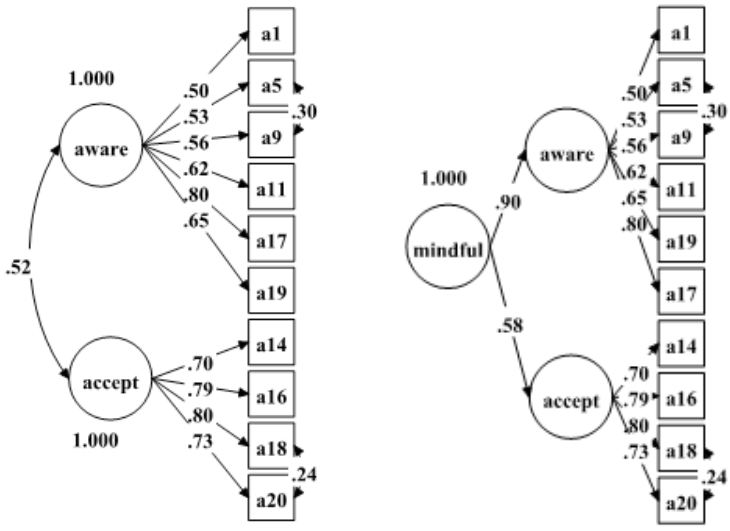


Fig 1. Structure model and second order CFA.
a1-a20: item1-20, one head arrow indicated loading factor, two heads arrow indicated correlation between item/domain

version that is the odd numbers for the awareness, and the others for the acceptance. The goodness of fit indices were all acceptable (CFI, TFI and RMSEA) and for the second order CFA, the SFR had high significant loading factor weights on mindfulness score in this group of samples. In general, people factors such as race, culture and meditation experiences impacted on construct validity.[10,26,27] Only one forth of samples had regular meditation practice, thus further investigation should be done in more experienced people that might have another structural result. The PHLMS-SFR could classify people with different meditation experiences in this sample group. Basically, the mindfulness assessment scale has an objective to assess mindfulness on daily activity which varies according to each person's perception. It had been observed that people without mindfulness meditation experience could not specify their own daily emotional experience correctly compared with those who meditated.[25] Duration of meditation practice was not analyzed in this study due to only a few cases (11.7%) had practice time more than 30 minutes.

PHLMS-SFR for both domains had significantly negative correlation to HAD which agreed with findings from Cardaciotto et al[6] and Zeng et al[10], that is, PHLMS had negative correlation to those of Beck Anxiety & Depression Inventory and also those of Chinese PHLMS and Chinese Positive and Negative Affect scale). The internal consistency and CITC were acceptable. It was noticed that composite reliability values were higher than those by Cronbach's alpha which considered each item as having the same weight and ignored the error in correlation between items. According to Kabat-Zinn and Theravada Buddhist concepts, mindfulness means accept and aware in each present moment[2,25] in order to reach equanimity of mind,[19] thus score of acceptance domain should be reversed in order to measure mindfulness practice. However, for positive thinking or avoidance as secular person, the score can be used directly.

CONCLUSION

The short version of PHLMS which was selected by researchers' opinion contained of 10 items which had a good psychometric property in the variety of samples such as student, care-givers, hospital personnel and medical cases which can be applied to evaluate mindfulness practice in daily life.

Limitation

The PHLMS short version which assessed daily mindfulness practice, was not for the purpose of diagnostic scale and was limited to people age above 17 years.

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Intracranial Black-Blood Vessel Wall Magnetic Resonance Imaging: Initial Clinical Experience in a Single-Center Study

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ABSTRACT

Objective: To assess the adjunct value of high-resolution black-blood vessel wall MR (VW-MR) imaging in the context of ischemic stroke and other vascular diseases in the clinical practice.

Methods: All patients with vascular abnormalities underwent MR on a 3T system. In addition to the conventional clinical scans, VW-MR imaging was performed by the volume isotropic turbo spin-echo acquisition (VISTA). Typical imaging parameters were: isotropic voxel size 0.35 × 0.35 × 0.35 mm^3. VW-MR findings in adjunction to MR angiography were reviewed by two neuroradiologists and presented as case series to compare with the final diagnosis based on the clinical data.

Results: 14 patients were recruited within 12 months, among which 12 completed MR scans. The final diagnoses included 6 cases of atherosclerotic plaque, 4 cases of aneurysm, 1 case of Takayasu vasculitis, and 1 case dissection. In general, VW-MR imaging before and after gadolinium allowed successful detection of vasculitis with circumferential smooth and thick enhancement, as well as active plaque with eccentric enhancement. Reasonable interpretation could be made for clot and thrombus with careful inspection of the clinical context. Signal void artifact could be observed in post coiling and stent placement arteries. Dark signal was also demonstrated in heavily calcified aneurysmal wall.

Conclusion: Despite relatively small sample size, our preliminary study has demonstrated the useful adjunct information provided by VW-MR imaging for diagnosis and characterization of intracranial vascular diseases in the clinical practice. Pitfalls should be aware in certain cases and large cohort clinical studies are warranted to further evaluate its clinical value.

Keywords: Vessel wall; intracranial artery; magnetic resonance imaging; black blood (Siriraj Med J 2018;70: 327-334)

INTRODUCTION

Imaging of intracranial vessels, especially arteries has been used in clinical practice for a long time. Conventional angiography with intraluminal catheterization is generally accepted as the standard imaging modality. With the development of computed tomography and magnetic resonance imaging, non-invasive techniques such as CTA or MRA have been proposed as alternative ways to demonstrate abnormality of the vessels especially intracranial arteries or veins. However, these luminal imaging cannot demonstrate the pathology at the vascular wall. For extracranial vessel wall imaging, ultrasonography and MRI have been tried for evaluation of carotid bifurcation disease such as vulnerable plaque in order to predict high risk of future stroke. The conventional MRI with suppression of flowing proton or so called black-blood technique has been proved histologically for tissue component of the abnormal signal and findings on multiple pulse sequences.[1] However, different scenarios for intracranial arteries are slower flow and smaller

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vascular size/wall. Also ethical issue makes it difficult to be conclusive from the imaging findings. Most recent reports were finalized with clinical context rather than direct comparison with pathologic result.[2]

With the new technology of MRI recently developed, it is possible for intracranial vessel wall imaging (VWI). The commercially available pulse sequence has been launched with improvement in image quality. At our hospital, we have evaluated the technique in clinical practice to consider the usefulness of the vessel wall imaging for intracranial arteries.

MATERIALS AND METHODS

This retrospective study was performed after approval from the Institute Ethical Committee (Si 396/2017). The subjects were recruited from the department PAC system for availability of vessel wall imaging and MRA. The MRI finding was retrospectively reviewed in consensus by two neuroradiologists without clinical data. Final conclusion of the diagnosis was summarized from clinical data. The result was presented as case series for the MRI findings and possible diagnosis.

MR imaging: The conventional brain imaging was performed as routine protocol of the institute. MRA was performed with 3D-TOF and contrasted enhanced MRA techniques for luminal imaging. Vessel wall imaging was performed with volume isotropic turbo spin echo acquisition (VISTA) technique (Philips, Best, the Netherlands). Since this study was a retrospective review, the pulse sequence used was varied according to the judgment of the radiologists on duty. All except case number 3, were performed with T2W-VISTA and gadolinium enhanced T1W-VISTA. Some cases were performed with PD-VISTA and some with T1W-VISTA. The parameters were shown in Table 1.

RESULTS

In total 14 cases underwent VW-MR imaging during 12 months. While 12 cases were obtained with complete clinical data, two cases did not have conclusive clinical data and were excluded for further assessment.

Among 12 cases, 8 cases of stroke were finally diagnosed as atherosclerotic plaque in 6 cases, Takayasu vasculitis in 1 case, and arterial dissection in 1 case. The other four cases were finally diagnosed as ruptured aneurysm in 1 case and unruptured in 3 cases. The demographic data of each case was presented in Table 2.

DISCUSSION

VW-MR imagings were successful in all cases.

Atherosclerosis

Case 1: Multiple small cortical infarction was demonstrated on cMRI. The VW-MRI showed enhancing eccentric enhancing plaque at the luminal narrowing M1 segment of right middle cerebral artery (MCA). Old pontine infarction was noted with irregular nonenhancing plaque at the adjacent basilar artery (BA).

Case 2 (Fig 1)**:** MRI brain showed no parenchymal lesion. VWI showed small focal enhancing plaque at M1 segment of right MCA with stenosis on MRA, compatible with active plaque.

Case 3: MRA showed focal stenosis of left posterior cerebral artery (PCA) with suspected ulceration. VWI showed small eccentric plaque with no ulceration. No contrasted VISTA was available due to low GFR.

Case 4 (Fig 2)**:** MRA showed mild stenosis of the distal basilar artery (BA). The rest of the BA was smooth normal

TABLE 1. MRI vessel wall imaging parameters.

	PD-VISTA (VIRTA)	T1-VISTA	T2-VISTA
Field of View (FOV) [mm^3]	200x165	200x251	150x150
Matrix size	304x252	268x336	228x156
Voxel size (acquired) [mm^3]	0.66x0.65x0.7	0.75x0.75x0.75	0.66x0.96x0.7
Voxel size (reconstructed) [mm^3]	0.35x0.35x0.35	0.37x0.37x0.38	0.35x0.35
Repetition time TR / echo time TE [msec.]	1450/33	700/33	2000/120
SENSE factor	2	1.7	2
Scan time [sec.]	5.30	6.45	5.26

Abbreviations: TR= repetition time; TE= echo time; PD= proton density; VISTA= volume isotropic turbo spin echo acquisition

TABLE 2. Demographic data of the cases.

Number	Age	Sex	History	Conclusive diagnosis
1	43	M	Left sided weakness for 1 day, previous history of repeated neurological deficit on left side more than 10 times in 2 weeks.	- Active plaque at right MCA with stenosis and Multiple cortical lacunar infarction – Non-active plaque at Basilar artery and old pontine infarct
2	37	F	Left hemiparesis for 5 minutes with fully recovery (TIA)	Right MCA plaque with stenosis.
3	80	F	Underlying hypertension presenting with gait ataxia with no other neurological deficit.	Left PCA plaque with mild narrowing
4	53	F	Previous pontine hemorrhage with right hemiplegia.	Short segment of mild distal basilar stenosis with Atherosclerotic plaque along the basilar artery.
5	38	M	Sudden onset of left hemiparesis. NCCT showed old lacunar infarction at right basal ganglion	Right MCA thrombosis with occlusion and old basal ganglion infarct.
6	51	M	Underlying hypertension presenting with left hemiparesis	Dolicoectasis with plaque along the left VA.
7	52	M	Incidental finding of abnormal intracranial arteries.	Right VA dissection.
8	18	F	Left hemiparesis and motor aphasia at age of 12 years old. Clinically diagnosed as Takayasu vasculitis.	Vasculitis of left ICA.
9	70	F	Subarachnoid hemorrhage	Right superior hypophysial aneurysm post coiling and residual neck
10	82	F	Left homonymous hemianopia and bilateral PCA infarction. Incidental finding of ACom aneurysm on CTA.	Post coiling AComA aneurysm with artifact.
11	73	F	Memory impairment with incidental finding of aneurysm at tip of BA on MRI brain.	Post coiling aneurysm at BA tip with stent placement in BA.
12	70	F	Fever with sinusitis with incidental finding of calcified aneurysm on CT.	Calcified aneurysm right M2 MCA

Abbreviations: M= male, F= female, AComA= anterior communicating artery, ICA= internal carotid artery, MCA= middle cerebral artery, PCA= posterior cerebral artery, VA= vertebral artery, BA= basilar artery, NCCT= non-contrast CT, CTA= CT angiography, TIA= transient ischemic attack

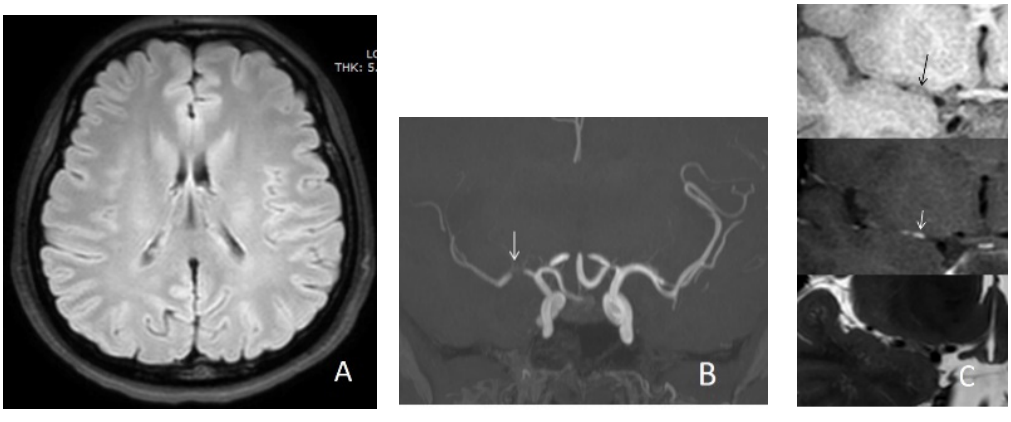


Fig 1. Case 2 patient with TIA. (A) no parenchymal lesion, (B) focal narrowing right M1 MCA (arrow), (C) VWI T1W(upper), Gd-T1W(middle) and T2W(lower) show enhancing plaque at the stenotic MCA.



Fig 2. Case 4 patient with pontine hemorrhage (A) T1W shows old hemorrhagic region, (B) MRA shows short segment of stenosis at basilar tip, (C) VWI T1W(left), Gd-T1W(middle), T2W(right) show irregular enhancing plaque along the basilar wall.

flow signal. VISTA showed multiple irregular eccentric plaque along the entire BA wall with mild enhancement.

Comments (Case 1-4): Intracranial atherosclerosis has been reported more in Asian stroke than western one. About 10% presented with TIA and 30-50% with ischemic stroke.[3] MCA is the most common site of atherosclerotic stenosis in Asian stroke.[4] Active plaque is generally defined as enhancement of the plaque.[5] However, no definite evidence has been reported about how long the culprit plaque has been enhanced.[6] We noticed enhancement of the plaque in most of our cases corresponding with the symptomatic brain supplied by the arterial lesions. Even more, case 2 (Fig 1) showed no detectable parenchymal lesion with repeated TIA, but abnormal vessel wall. This may be useful information for confirming ischemic process rather than local convulsive process. Intensive medical treatment has been reported regression of the stenosis and plaque enhancement at the symptomatic side.[5,7] VWI may be useful for decision in medical treatment and follow up of the treatment outcome. Case 4 (Fig 2) also showed additional information of VWI on MRA. Luminal imaging may not explain the etiology of the stroke like hemorrhagic pons in case 4 in which more pathology was seen to be more extensive on VWI.

On VWI, the most common pattern of small intracranial atherosclerotic plaque is eccentric.[8] MCA is the most common artery with intracranial atherosclerotic plaque. Common location of MCA culprit plaque is opposite to the perforator orifice or just at the origin of the branches.[9]

Case 5 (Fig 3)**:** A 38-year-old male with acute left hemiparesis and old basal ganglion infarction on CT underwent mechanical thrombectomy. The endovascular procedure was performed at the occluded right MCA with yielding of small amount of white clot. Recanalization of the right MCA was achieved with irregular narrowing of the lumen. Followed up MRI showed occlusion of the right MCA. VWI demonstrated high signal clot in the lumen with irregular enhancement, possible mixed organized and non-organized thrombus, as well as active plaque.

Summary of signal appearance on VW-MR images of cases 1-5 was shown on Table 3.

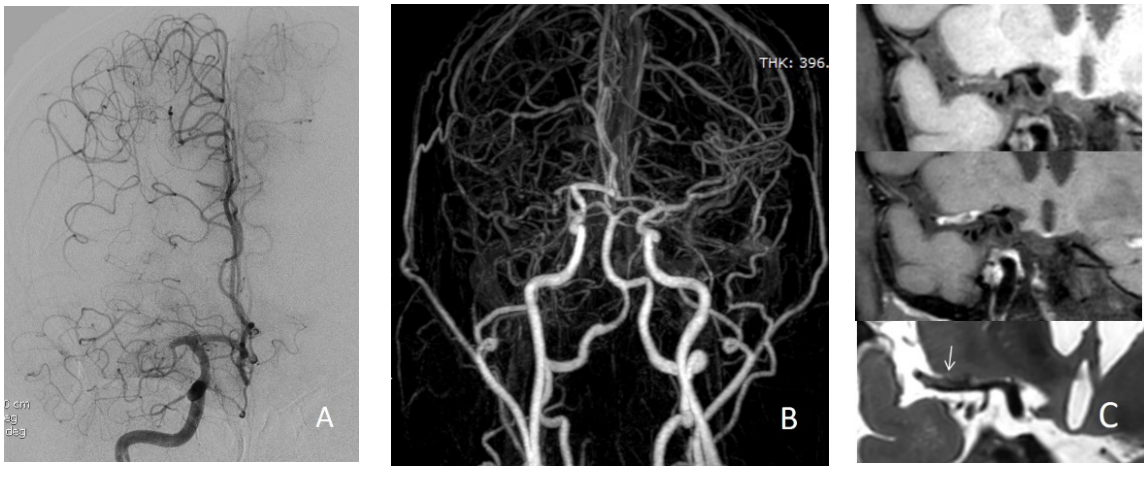


Fig 3. Case 5 patient with acute stroke. MRI showed old infarction at right basal ganglion (not shown). (A) DSA shows occlusion of right MCA with scanty clot from mechanical thrombectomy. (B) MRA still shows occlusion right MCA. (C) VWI T1W (upper), Gd-T1W(middle) and T2W(lower) show thrombus with irregular enhancement.

TABLE 3. Signal intensity of lesions in case 1-5 on vessel wall imaging.

Case number/location of lesions	VISTA-T1W	VISTA-T2W	Gd-VISTA-T1W (enhancement)
Right MCA	Iso-SI	Low-SI	Positive
Basilar artery	Iso-SI		Negative
Right MCA	Iso-SI	Iso to increased SI	Positive
FU 4 months	Low-SI	Iso-SI	Positive
Left PCA	Iso-SI	NA	NA
Basilar artery	Iso-SI	Low-SI	Positive
Right MCA	High and iso-SI	Iso-SI	Positive

Abbreviations: SI= signal intensity; NA= no information/not done

Comment (Case 5): The component of plaque in intracranial atherosclerotic stenosis (ICAS) cannot be separated as in neck arteries due to small lesion out of MRI resolution.[10] Variable signal intensity has been noted even in cervical carotid artery.[10-14] Lipid core may have low or iso-SI onT1W and T2W due to component of cholesterol and rich-water proton.[15,16] Signal intensity of blood component on VISTA is not so familiar for radiologists, unlike conventional T1W or T2W. By solely using high signal T1W as the symptomatic plaque is not reliable by visual assessment.[17] Low signal on T2W and SWI was also reported helpful for identifying hemorrhagic plaque.[10] Generally, enhancing plaque is accepted as the most reliable marker for unstable and symptomatic stroke.[5] The careful point is misinterpretation of periarterial enhancement from vessel of the adjacent meninges.[18,2,19]

However, case 5 demonstrated mixed high and iso-signal of the blood which was believed to be subacute or chronic stage of the inflammatory thrombus with organization. The enhancement of the clot was difficult to separate from plaque at the wall of the small size artery. With history of relapsed stroke and old infarct in this case, atherosclerotic plaque was believed to be the cause of severe stenosis and explained yielding of scant clot in thrombectomy.

Arterial Dissection

Case 6: DSA showed dilatation of left intracranial vertebral artery. No definite intraluminal flap was detected. VWI showed thick wall with mixed high and iso signal nearly circumferentially. The wall was also enhanced suggestive of active process. No definite intimal flap was detected.

Case 7: DSA showed multiple areas of intracranial arterial stenosis. The most severe was noted at right VA with post-stenotic dilatation. VWI was requested for possible dissection. MRA showed sharp linear filling defect inside the irregular lumen, not artifact. VISTA confirmed the enhancing intimal flap, compatible with dissection.

Comments (Cases 6-7) (Fig 4): Intracranial arterial dissection has been found more in young adults and more in Asian population than Europeans.[20-22] Definite diagnosis of arterial dissection is present intimal flap and two lumens or change of characters after follow up.[23] The criteria may not be true for intracranial dissection. Many cases may have no symptoms for immediate diagnosis at time of event.[24] Most reported imaging findings included multistages of the disease. Thrombosed false lumen may be seen as high signal clot at the wall, either eccentric or circumferential location, and compromise the true lumen.[25] After healing, the lumen may be back to original size or dilated.[26] To separate from atherosclerosis, dilatation was used to be believed the clue. However, more evidence of remodeling of intracranial atherosclerotic arteries has shown this concept might not be true.[5,27] We demonstrated two cases with diagnostic problem of dissection. Case 7 clearly showed the intimal flap. For case 6, the circumferential high signal wall may represent vulnerable atherosclerotic plaque or thrombosed false lumen. Dilatation of the vertebral artery may be the process of remodeling which has been found more in posterior circulation.[27] Surprisingly, both cases had no symptom from the involved arteries. Positive remodeling is suggestive of high risk, whereas negative one is more compatible with fibrotic healing process.[27]

It should be emphasized that when dilated artery or intramural hematoma is found, diagnosis of arterial dissection should be cautioned. Given the differential diagnosis for both dissection and atherosclerosis it may be more proper to suggest follow up imaging to observe if any change of the lesion feature, is reported.

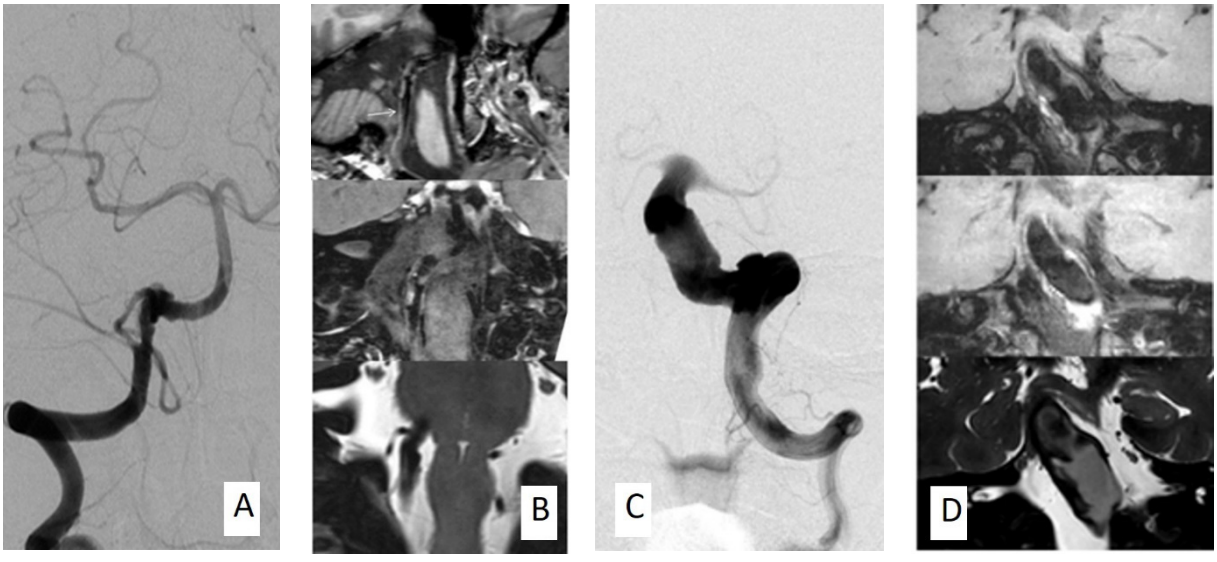


Fig 4. Case 6 (A, B): left atherosclerotic plaque and positive remodeling left vertebral artery. (A) DSA, (B) VWI shows irregular plaque with hemorrhage component and enhancement along the VBA wall. ; Case 7 (C, D) dissection of right VA. (A) DSA, (B) VWI T1Wshows enhancing intimal flap (arrow) of right VA.

Vasculitis

Case 8 (Fig 5)**:** Known case of Takayasu vasculitis showed left MCA infarction and occlusion left supraclinoid ICA causing developed Moya-like pattern The VWI was performed 6 years after the event and showed small left ICA with thick enhancing wall at the petrous and cavernous part, suggestive of active process.

Comment: Usually, CNS involvement in Takayasu vasculitis is in large extracranial arteries. Involvement of intracranial artery was reported in 15.2% and 7.6% was vasculitis.[28] Moya-like pattern is rarely reported.[28,29] Arterial wall edema was reported in Takayasu vasculitis in 94% of clinically active disease and 56% in clinically inactive disease.[30]

Vasculitis has been well demonstrated with VWI. Circumferential smooth and thick wall enhancement is the clue for diagnosis.[31] Dilated neovasculature has been demonstrated in arterial wall of Takayasu arteritis.[32, 33] Evidence of thinning media of arterial wall and finally luminal stenosis (vanishing MCA) was reported in idiopathic Moyamoya disease.[34] In Takayasu arteritis, involvement starts at adventitia and progresses to intima. We demonstrated rare Moya-like Takayasu arteries with VWI. The stenotic ICA was totally occluded with no enhancement, suggestive of inactive process. However, the rest of more proximal ICA was still enhanced, and so probably active disease. Small arterial size of the involved ICA implied the same process as reported in iMoyamoya disease, or less functional artery. With the history of the patient, the diagnosis is usually in no doubt if arterial stenosis is seen. VWI might be useful for areas with no luminal stenosis to demonstrate active process like this case.

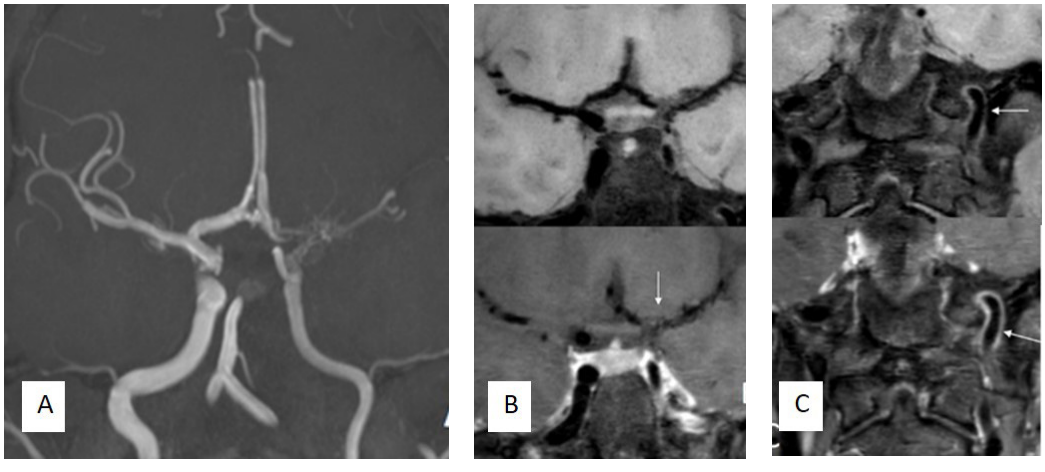


Fig 5. case 8 patient with Takayasu arteritis (A) MRA shows severe stenosis of left distal ICA with moya-like pattern, (B) VWI shows no enhancement of the arteries around the stenotic left ICA (arrow), but enhancement of wall along the more proximal left ICA is noted (arrow in C) and small size of the artery.

Aneurysm and instrument placement

Case 9: DSA showed right superior hypophyseal aneurysm before and after coiling. VWI showed small focal signal void at the aneurysm site with wall enhancement. CE-MRA confirmed small residual neck of aneurysm at the lesion.

Case 10: DSA showed before and post coiling aneurysm at left anterior communicating artery. VWI showed signal void of the aneurysm, suggestive of patent lumen. The aneurysmal wall showed no definite enhancement. However, CE-MRA showed no residual lumen of the aneurysm. This might be artifact from coil on VISTA.

Case 11 (Fig 6)**:** DSA showed post coiling basilar tip aneurysm with stent placement in BA. VWI showed signal void of the BA lumen which appeared larger than demonstrated on CE-MRA. This may be blooming effect from stent in the basilar lumen. The BA wall was enhanced suggestive of inflammatory process. The coiling aneurysm was heterogeneous signal on both VISTA and CE-MRA. Aneurysmal wall enhancement was clearly seen.

Case 12 (Fig 7)**:** Incidental finding of calcified aneurysm at right M2 MCA on CTA. VWI showed patent lumen of the aneurysm. The calcification appeared dark on VISTA. No enhancement of the aneurysm wall implied an inactive one.

Comment (Cases 9-12): VWI has demonstrated thick peripheral wall enhancement in ruptured aneurysm and predicted high risk ruptured one.[35,36] We demonstrated one large calcified aneurysm at right MCA with no enhancement of the wall (case 12). This might suggest low risk rupture. We have been following up this patient up to now. For the other cases, the study was performed after coiling. Enhancing aneurysmal wall might be from foreign material or manipulation during intervention.

Patent vascular lumen is dark signal on VISTA. Calcification is also dark signal on VWI.[1] However, metallic material could cause signal void too which was demonstrated in cases 10 and 11. Using VWI for follow up of aneurysmal lumen in post coiling or stenting should be considered. Up to our current knowledge, this finding has not been reported yet.

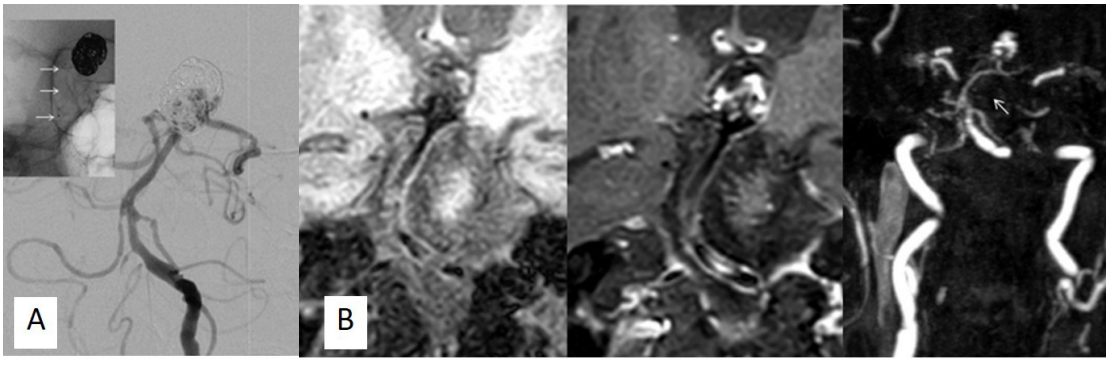


Fig 6. Post coiling aneurysm (A) DSA of case 11 shows coiling and stent in the aneurysm and basilar artery, (B) VWI T1W(left), Gd-T1W (middle) demonstrate patency of the BA not corresponding with stenotic lumen on CE-MRA(right).

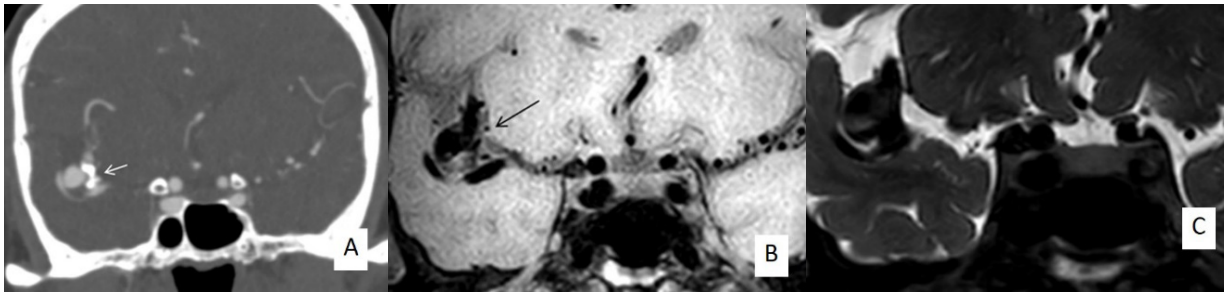


Fig 7. Case 12 patient with calcified aneurysm at right MCA (A) CT shows calcification at the wall of the aneurysm, (B, C) VWI show low signal of the calcification which may be missed as patent lumen.

CONCLUSION

Vessel wall imaging with MRI is a useful method for demonstrating the pathophysiology of the intracranial vascular disease. The findings add on the information in clinical management of the patients. With advancement of the MR technology, better high resolution of the vascular wall would be achieved. Important pitfalls should be aware in selected cases. Radiologists should get familiar with the signal of the findings and inform the clinicians that the technique is not validated yet. Clinical context is still highly needed for final conclusion.

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Endometrial Thinning after Ovarian Stimulation using Letrozole or Clomiphene Citrate: A Randomized Trial

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ABSTRACT

Objective: To compare endometrial thickness after three consecutive cycles of ovulation induction with clomiphene citrate versus letrozole.

Methods: Eighty-four women with normal menstrual interval who attended the university infertility clinic from June 2016 to March 2017 were eligible for the study. After the endometrial thickness of baseline cycle was recorded, all participants were randomized into two groups of clomiphene citrate or letrozole treatment for three consecutive cycles. Endometrial thickness and estradiol level were measured when at least one follicle reached 17 mm in diameter. The differences in endometrial thickness relative to baseline of the two groups were compared.

Results: A total of 62 patients completed three cycles of ovarian stimulation. Both drugs resulted in significantly thinner endometrium compared with the baseline cycle thickness. The mean endometrial thickness was significantly decreased in the clomiphene citrate group compared with letrozole group (7.46 ± 1.71 vs 8.88 ± 2.34 mm, $p = 0.029$). Estradiol level on the day of induced ovulation was significantly higher in the clomiphene citrate group than in the letrozole group (706.0 (207.9, 2209.0) vs 168.7 (30.0, 401.8), $p < 0.001$). The number of the follicles reaching 17 mm on the day of induced ovulation was higher in the clomiphene citrate group (1.9 ± 0.8 vs 1.4 ± 0.5, $p = 0.002$).

Conclusion: Letrozole had less effect on endometrium thinning after three consecutive cycles of induced ovulation compared with clomiphene citrate.

Keywords: Clomiphene citrate; letrozole; ovulation induction; endometrial thickness; consecutive cycles (Siriraj Med J 2018;70: 335-342)

INTRODUCTION

Ovulation induction combined with intrauterine insemination (IUI) provides a treatment for infertility caused by anovulation or unexplained infertility. It is safe, efficient and inexpensive. However, the fecundity rates varies from 15-22 percent,[1] and optimal rates require repeated treatments. Clomiphene citrate (CC) is the major medicine used for ovulation induction. It is a racemic mixture of zuclomiphene and enclomiphene.[2] Zuclomiphene is the most anti-estrogenic component and mildly estrogenic, whereas enclomiphene is entirely anti-estrogenic. Clomiphene citrate competitively binds to the estrogen receptor in the hypothalamus and pituitary, leading to the alleviation of the negative feedback exerted by endogenous estrogen, and alters the characteristics of pulsatile gonadotropin releasing hormone secretion,[3] which results in the elevation of production and secretion of follicle-stimulating hormone (FSH) from pituitary. Unfortunately, this antagonistic effect on estrogen receptors does not only exist in the hypothalamus, but

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also throughout the body, especially in the endometrium and endocervix. As a result, the estrogen antagonist effect of CC disturbs endometrial growth and maturation.[4]

The metabolism of CC varies between individuals and is related to body weight.[5] Women weighing 45-59 kg have become pregnant using 50 mg/day CC.[6] The circulating half-life of CC ranges from 27.5-38.5 days, and serum concentrations of zuclomiphene remain at least 10% of peak levels after 28 days post-ingestion of a single 50 mg tablet.[7] The effect of repetitive administration of a 50 mg tablet at 28-day intervals is cumulative, resulting in a 50% increase in basal CC levels per month.[7] Accumulation of CC or metabolites in endometrium may affect the pregnancy outcome and preclinical abortions.[2]

Letrozole was proposed to be an alternative to CC for ovulation induction.[8] It is an aromatase inhibitor that prevents the conversion of androgen to estrogen. The resulting elevated level of intra-ovarian androgen is positively associated with the expression of FSH receptor mRNA in small antral follicles,[9] which have enhanced sensitivity to FSH stimulation. The circulating half-life of letrozole is only 42 hours, which is not affected by age.[10] Pharmacodynamic analysis suggested that letrozole had no effect on endometrial thickness and cervical mucus, but improved folliculogenesis.[11] A systematic review and meta-analysis indicated that a significant increase in live birth and pregnancy rates was observed in letrozole-treated compared with CC-treated polycystic ovarian syndrome patients.[12] In 2016, the American Congress of Obstetricians and Gynecologists recommended that letrozole be considered a first-line therapy for ovulation induction in polycystic ovarian syndrome patients.[13] The different pregnancy rates between the CC and letrozole groups may due to drug effects on endometrial thickness.[14, 15]

Some researchers found that thin endometrium caused lower pregnancy rates.[16,17] No pregnancy occurred if the endometrial thickness was less than 6 mm.[17] This suggested that endometrial thickness is one of the key factors involved in successful insemination cycles. Several studies reviewed the effect of CC and letrozole on endometrial thickness, but the results were controversial.[18-22] Some evidence indicated that repeated use of CC decreased endometrial thickness.[17] However, no study has compared the cumulative effect of letrozole versus CC on endometrial thickness. Therefore, the main objective of this study was to compare endometrial thickness after three stimulation cycles using CC or letrozole. Secondary objectives were to compare endometrial thickness on the day of induced ovulation between the third and baseline cycle of each drug; and to compare estradiol levels and the number of follicles ≥17 mm on the day of induced ovulation in each cycle.

MATERIALS AND METHODS

Subjects and procedures

The study was conducted between June 2016 and March 2017 at the university infertility clinic and was approved by the Hospital Institutional Review Board (Si 371/2016). Recruited patients were aged 18-42 year old and recommended for IUI and had a normal menstrual cycle interval (defined as 21 to 35 days per cycle or at least nine menstrual cycles per year) and no previous treatment. Those with endometrial lesions or bilateral fallopian tube obstruction were excluded. Patients who had used oral contraceptive drugs within one month, or depot medroxyprogesterone acetate/GnRH agonist depot within six months before enrollment were also excluded. Informed consent was obtained before the trial.

The baseline blood test included day 3 hormones (FSH, estradiol, luteinizing hormone (LH), and prolactin), serologic blood test (Anti-HIV, VDRL, HBsAg) and hemoglobin typing. Tubal patency was confirmed by hysterosalpingography. Transvaginal ultrasound was performed to screen endometrial abnormalities, such as lesions in the uterine cavity. Serial ultrasound was performed by one trained gynecologist who was blinded to the protocol, to check for the dominant follicle every other day starting from day 10 ± 1 of the menstrual cycle. When the dominant follicle reached 17 mm in diameter, serum estradiol levels were assessed, ovulation was induced on the same day, and endometrial thickness and number of follicles above 17 mm were subsequently recorded. Urine pregnancy tests were performed 14 days after IUI or timed intercourse. Patients whose follicle failed to reach 17 mm in diameter on day 21 of the menstrual cycle, or those pregnant at the baseline cycle, were excluded. The remaining participants were randomized into two groups at the beginning of the second cycle, using computer generated randomization numbers allocated at a ratio of 1:1 by the research nurse and sealed in individual envelopes. The first group received 50 mg/day CC (Ovamit®, Remedica Ltd., Cyprus), and the other group received 2.5 mg/day letrozole (Letov®, Cadila Healthcare Limited, India). The medication was commenced on the third day of the menstrual cycle and continued for five days. Participants then had transvaginal ultrasound, hormonal assessment and ovulation induction, as described above in the baseline cycle. Data was analyzed for participants who received medication for three consecutive cycles.

Transvaginal ultrasound

Endometrial thickening was measured using a 7.5 MHz transvaginal transducer (Prosound α 7, Aloka Co., Ltd, Tokyo, Japan). Endometrial thickness was measured from the echogenic junction between endometrium and myometrium, from one side to the opposite side at the point of maximal thickness, with the uterus in a central longitudinal axis. The depth magnification was adjusted until the uterus covered about two-thirds of the sonographic view. Follicular diameter was documented by calculating the mean of the two perpendicular diameters measured at the largest plane of the follicle.

Sample size

Sample size was calculated based on the study of Angel et al.,[23] who reported the endometrial thickness was 7.47 mm and 8.56 mm in the CC and letrozole groups, respectively. Therefore, using 5% and 20% type I and II errors, respectively, and a 20% dropout rate, each group required a sample size of 45 patients.

Statistical analysis

Statistical analysis was performed using PASW Statistics 18. Continuous data was expressed as mean ± SD for a normal distribution, or median with range if non-normal. Categorical data was expressed as percent. The unpaired T-test or Man-Whitney U test were used as appropriate. Differences in endometrial thickness between two groups were calculated using the linear mixed model, using intention to treat analysis. All tests of significance were two-tailed with p value < 0.05.

RESULTS

One hundred and thirty-two participants were screened, and 97 participants were eligible to undergo baseline evaluation (Fig 1). After the baseline evaluation, 13 cases were excluded. The remaining 84 patients were randomized into two groups. After further exclusion because of loss of follow-up or pregnant participants during the first 2 cycles, a total of 31 cases in each group continued receiving the third cycle of stimulation.

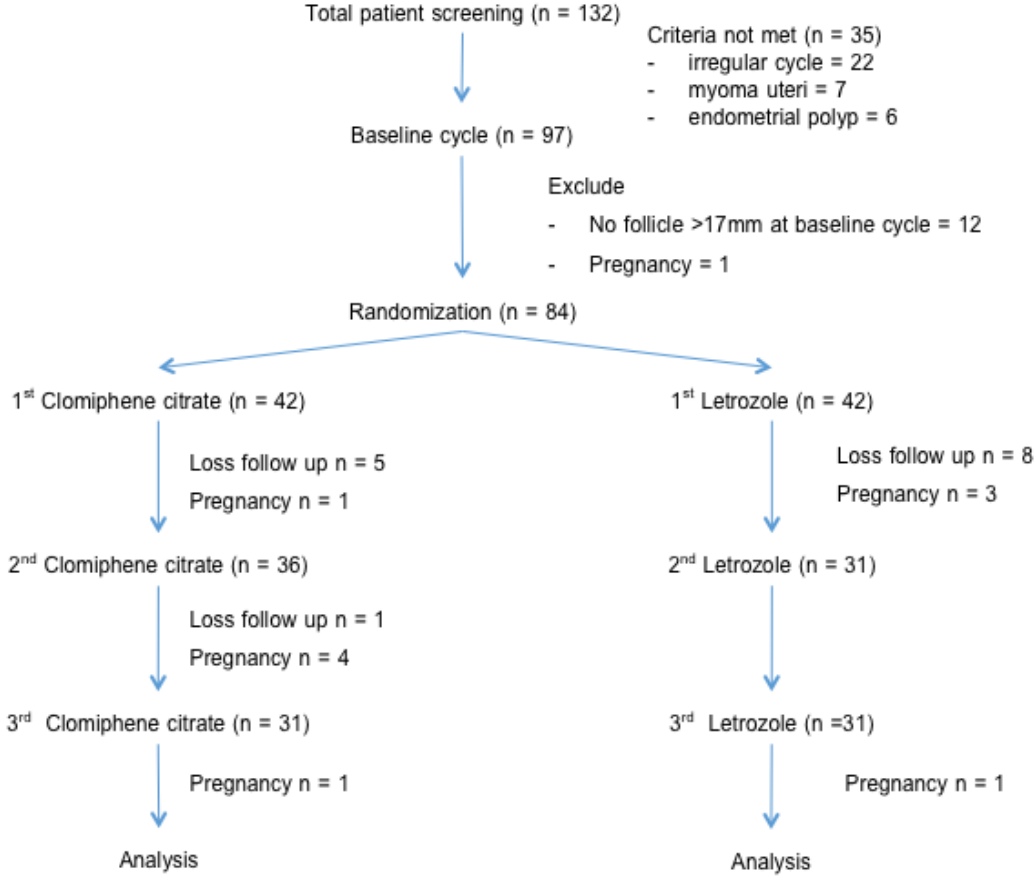


Fig 1. Flow and randomization of participants.
A total of 132 patients were screened, 97 were eligible for baseline evaluation. Thirteen patients were excluded before randomization due to pregnancy or no presence of dominant follicle. Eighty-four patients were equally randomized into two groups, the clomiphene citrate group (CC) and the letrozole group. In the CC group, 6 and 5 patients were excluded from the study at cycle 1 and 2, due to loss follow up or pregnancy. In the letrozole group, 11 patients were excluded from the first cycle because of loss follow up and three pregnancies. There were 31 patients left in each group at cycle 3.

The baseline characteristics of participants are displayed in Table 1. There was no difference in mean age, BMI, cycle interval, duration of marriage, type of infertility, and baseline FSH, LH and estradiol levels between the two groups. Baseline cycle characteristics are shown in Table 2. The endometrial thickness on the day of induced ovulation, the number of dominant follicles and serum estradiol levels were not statistically different between groups.

Endometrial thickness on the day of induced ovulation for each menstrual cycle of both groups is shown in Fig 2. The CC group seemed to have a progressive reduction in endometrial thickness when CC was used repeatedly. During letrozole treatment, endometrial thickness was reduced compared with the baseline cycle, but the level of reduction remained constant over the three stimulation cycles. Overall, endometrial thickness for each group in all stimulation cycles was significantly reduced compared with the baseline level. There was no difference in endometrial thickness between the CC and letrozole group for the first and second stimulation cycles (Table 2). However, in the third stimulation cycle, endometrial thickness was significantly reduced in the CC group compared with the letrozole group (7.5 ± 1.7 and 8.9 ± 2.3 cm, respectively, $p = 0.008$). The difference remained significant when adjusted for other potential factors (i.e., age, BMI, type of infertility, and duration of marriage) (Table 3). There were seven participants (22.6%) in the letrozole group, and 12 participants (38.7%) in the CC group exhibiting endometrial thickness less than 7 mm on the day of induced ovulation in the third stimulation cycle ($p = 0.27$).

There were significantly higher levels of estradiol and more follicles with > 17 mm diameter in the CC group for every stimulation cycle as shown in Table 2.

DISCUSSION

Endometrial thickness is one of the crucial factors affecting pregnancy rate.[16,17] Thinner endometrium has a reduced functional layer, resulting in an implantation site closer to the spiral arteries of the basal layer, which contains high blood flow and oxygen tension. This situation facilitates the production of reactive oxygen species (ROS), leading to interrupted embryonic development and implantation.[24,25] In addition, the resistance index of uterine and radial artery blood flow was high in endometrium of reduced thickness, so glandular epithelium growth was impaired and expression of endometrial vascular endothelial growth factor was reduced, limiting endometrial growth.[26] Thin endometrium may result from several factors, including anti-estrogenic effects of CC,[27] adhesion after endometrial curettage,[28] long-term (>10 years) combined oral contraceptives[29] and idiopathic causes.

TABLE 1. Baseline characteristics between clomiphene citrate (CC) and letrozole groups.

	CC (n=31)	Letrozole (n=31)	P-value
Age (years)	34.9 ± 3.2	36.2 ± 3.1	0.105
BMI (kg/m^2)	21.4 ± 3.0	22.6 ± 4.9	0.249
Cycle interval (days)	29.3 ± 2.9	29.7 ± 3.0	0.496
Duration of marriage (years) †	4 (1-14)	4.5 (1-12)	0.297
Characteristics of infertility ‡			
Primary	27 (87.1%)	27 (87.1%)	1.000
Secondary	4 (12.9%)	4 (12.9%)	
Baseline FSH (mIU/mL)	7.4 ± 1.8	7.6 ± 3.3	0.685
Baseline LH (mIU/mL)	4.6 ± 1.9	5.3 ± 2.4	0.226
Baseline E_2 (pg/mL)	39.8 ± 19.9	34.8 ± 18.3	0.311

Data shown as mean ± SD
†shown as median (minimum-maximum)
‡shown as n (percent)

TABLE 2. Effects of ovulation induction in clomiphene citrate (CC) and letrozole groups. Most data show as mean ± SD.

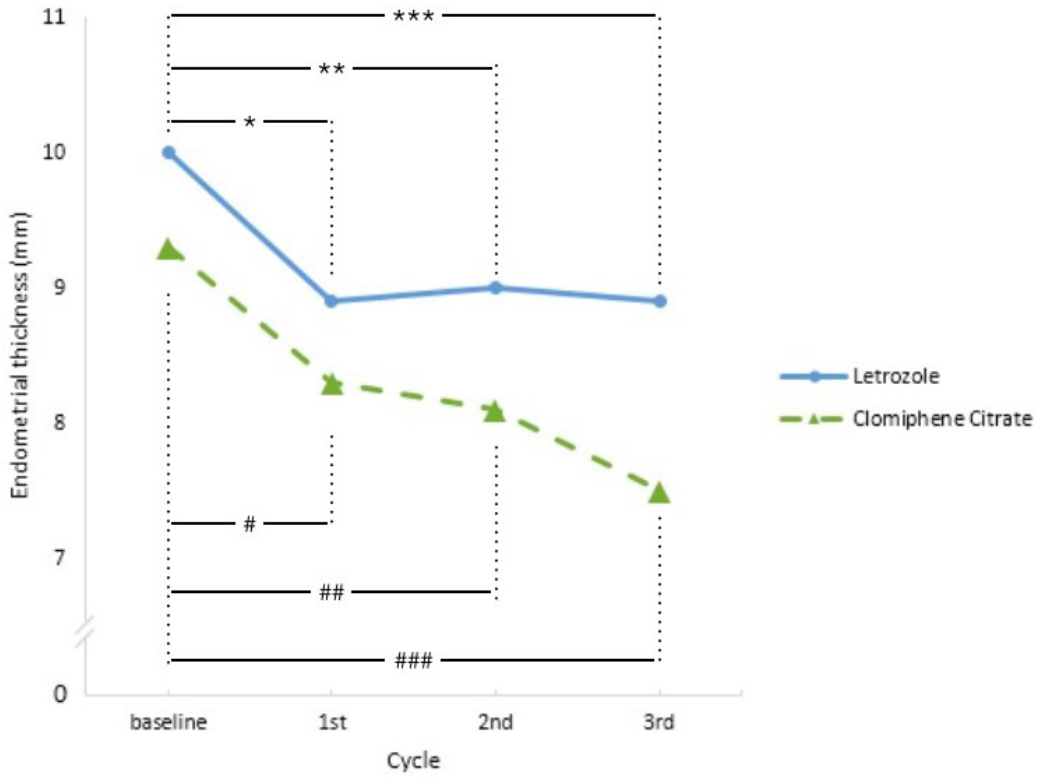
Baseline cycle	CC (n=31)	Letrozole (n=31)	P-value
Endometrium thickness (mm)	9.4 ± 2.1	10.0 ± 2.2	0.205
Number of follicle ≥ 17 mm	1.0 ± 0.2	1.0 ± 0.18	0.561
Estradiol level† (pg/ml)	252.4 (5.0 - 808.5)	238.2 (13.4 - 1195.0)	0.795
Size of dominant follicle (mm)	18.6 ± 3.0	17.8 ± 1.5	0.198
1st cycle stimulation			
Endometrium thickness (mm)	8.3 ± 2.5	8.9 ± 2.0	0.301
Number of follicle ≥ 17 mm	1.8 ± 0.8	1.2 ± 0.4	<0.001*
Estradiol level† (pg/ml)	825.0 (211.0 – 1997.0)	173.9 (32.1 – 360.8)	<0.001*
Size of dominant follicle (mm)	20.0 ± 2.9	19.9 ± 3.6	0.954
2nd cycle stimulation			
Endometrial thickness (mm)	8.1 ± 2.0	9.0 ± 2.4	0.119
Number of follicle ≥ 17 mm	2 ± 1.0	1.3 ± 0.6	0.003*
Estradiol level† (pg/ml)	938.9 (234.8 - 1887.0)	146.0 (48.0 - 336.6)	<0.001*
Size of dominant follicle (mm)	20.3 ± 3.0	19.3 ± 5.2	0.362
3rd cycle stimulation			
Endometrial thickness (mm)	7.5 ± 1.7	8.9 ± 2.3	0.008*
Number of follicle ≥ 17 mm	1.9 ± 0.8	1.4 ± 0.5	0.002*
Estradiol level† (pg/ml)	706.0 (207.9 – 2209.0)	168.7 (30.0 – 401.8)	<0.001*
Size of dominant follicle (mm)	19.7 ± 3.2	20.9 ± 3.0	0.142

† Data shown as median (min-max)
*Statistically significance

TABLE 3. Difference of endometrial thickness at the end of the 3rd cycle stimulation of both drugs.

Endometrial thickness (mm), mean (SD)	Baseline	Cycle 1	Cycle 2	Cycle 3	Adjust MD†	95% CI	P-value
CC (n=31)	9.4 (2.1)	8.3 (2.5)	8.1 (1.9)	7.5 (1.7)	0.97	(0.1,1.84)	0.029*
Letrozole (n=31)	10.1 (2.2)	8.9 (2.1)	9.0 (2.4)	8.9 (2.3)			

† Adjusted by age, BMI, type of infertility, duration of marriage
* Statistically significance



* p= 0.029, ** p=0.043, *** p= 0.021,
# p= 0.042, ## p= 0.03, ### p= 0.01

Fig 2. Relation between endometrial thickness between each menstrual cycle of both drugs.
The CC group had a continuous reduction of endometrial thickness when used repeatedly. In the letrozole group, the endometrial thickness was diminished compared with the baseline cycle; however the reduced thickness level remained constantly over the three stimulation cycles. Overall, endometrial thickness for each group in all stimulation cycles was significantly decreased compared with the baseline level.

In the present study, we found that endometrial thickness was significantly decreased after three consecutive stimulation cycles in the CC compared with letrozole group. The decrease remained significant after adjustment for other potential factors. Some randomized studies reported a similar finding in a single cycle treatment,[20,30] although this result was contrary to other earlier findings.[31-33] A systematic review and meta-analysis found no significant difference in endometrial thickness between CC and letrozole administration for unexplained infertility.[18] In that analysis, six randomized studies were included, although only four studies reported endometrial comparisons.[20,22,30,31] The cumulative effect of these treatments on the endometrium during consecutive ovarian stimulation had not been previously examined. In this study, an accumulated deteriorative effect on endometrial thickness was detected in the CC group after three repeated stimulations. This may be due to the cumulative effect of the antagonist function of CC on estrogen receptors. The alpha and beta estrogen receptors are expressed differently in various tissues. Estrogen receptor β (ERβ) is the prevalent estrogen receptor in brain and cardiovascular systems, while estrogen receptor α (ERα) predominates in the uterus, especially during the proliferative phase of the menstrual cycle.[34] In the uterus, CC acts as an estrogen agonist/antagonist via ERα, in an estrogen concentration-dependent manner; whereas it acts as a pure estrogen antagonist via ERβ.[35] Therefore, CC enhances the secretion of pituitary gonadotropins, but attenuates the estrogen effect on ERα in the uterus and cervix. Young et al.,[36] showed the rise of serum zuclomiphene citrate levels through four consecutive cycles of CC administration. The long half-life of zuclomiphene may cause endometrium thinning by antagonistic effects on ERα, especially when used repeatedly.[36] Accordingly, the thinning of endometrium in the CC group is likely caused by the anti-estrogenic effect of zuclomiphene.

In the letrozole group, endometrial thickness was also reduced in stimulation cycles compared with the baseline cycle. Considering the half-life or clearance rate of letrozole (around 42 hours), it takes approximately 10 days for letrozole metabolization and clearance from serum.[10] Therefore, during a normal menstrual cycle interval (21-35 days), serum estradiol levels became low on the day of induced ovulation compared with the

baseline cycle, leading to endometrial thinning. Letrozole is effectively metabolized before the commencement of the next cycle, resulting in a smaller cumulative effect. Therefore, endometrial thickness in the stimulation cycles was lower than the baseline value, but remained at a similar level in all three consecutive cycles.

The definition of thin endometrium varies from less than 5 to 8 mm.[37] The recommended follicular phase endometrial thickness, which is positively associated with pregnancy outcome, is 7 mm.[37,38] Past research found no pregnancy occurred when endometrial thickness was less than 6 mm.[17] In the current study, an equivalent number of participants had endometrial thickness less than 7 mm in the CC and letrozole groups (12 (38.7%) vs 7 (22.6%), respectively). Surprisingly, one pregnancy in the CC group occurred despite an endometrial thickness of only 4.9 mm, resembling a similar case that conceived via IUI with an endometrial thickness of 4 mm.[39] Though endometrial thickness is one of the key factors involved in pregnancy success during insemination cycles, it may not be the only important factor to consider.

This is the first study to compare the effect of consecutive cycles of CC and letrozole on endometrial thickness. Our study has some limitations to consider. Firstly, only one dose of each drug was examined, and the longer-term effect of higher doses, especially for CC, remains unknown. Secondly, the primary objective of the study was endometrial thickness, and pregnancy and live birth rates were not assessed. Further study should be encouraged to evaluate the later outcomes. Third, endometrial receptivity in thin endometrium was not studied. More molecular studies are required to discover the underlying mechanisms.

In conclusion, CC had a more cumulative detrimental effect on endometrial thickness than letrozole after repetitive administration. Letrozole may be considered instead of CC in later cycles to limit the degree of endometrial thinning.

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A Retrospective Study of the Effects of Craniospinal Irradiation (CSI) on Height in Children with Brain Tumor

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ABSTRACT

Objective: To compare height standard deviation score (SDS) at start of radiation therapy and at the last follow-up in children with brain tumor treated with CSI.

Methods: This study is a retrospective study. Medical records of children aged 3-15 years old, diagnosed with embryonal or germ cell tumor, and treated with 3D conformal radiation therapy (3DCRT) for CSI at Division of Radiation Oncology, Siriraj Hospital between 2006 and 2014 were reviewed. Patient's demographic data, clinical information, radiotherapy technique, weight and height before the start of radiation therapy and at follow-up were obtained. The height standard deviation score (SDS) was calculated by INMU-Nutri Stat software program.

Results: There were twenty one eligible patients. Overall, the latest height SDS was significantly reduced. Mean reduction of the height SDS was 1.24 ± 1.08 ($p < 0.001$). Four patients (19%) had the latest height SDS < -2. Positive correlation between initial height and the latest height ($p = 0.001$), and negative correlation between hypothalamic-pituitary axis (HPA) mean dose and the latest height ($p = 0.02$) were found. The patients who received HPA mean dose more than 47Gy tended to have the latest height SDS less than -1.5.

Conclusion: Children treated with CSI have significant reduction of height even 3D-CRT was used. The incidence of short stature is 19%. The initial height is strongly related to the latest height. Weak negative correlation of radiation dose to HPA and the latest height was observed.

Keywords: Craniospinal irradiation; growth height; medulloblastoma; germ cell tumor (Siriraj Med J 2018;70: 343-348)

INTRODUCTION

Craniospinal irradiation (CSI) is standard treatment for childhood brain tumors with neuraxis dissemination or with high propensity of neuraxis dissemination, including most embryonal tumors and some germ cell tumors. Embryonal tumors include medulloblastoma (MB), supratentorial primitive neuroectodermal tumor (sPNET), atypical teratoid/rhabdoid tumor (AT/RT), pineoblastoma, and others. Both embryonal tumors and germ cell tumors are treated with combined modality approaches: surgery, radiation therapy (RT), and chemotherapy. The side effects attributed to radiation is of primary concern for patient with brain tumor treated with CSI. Due to prolonged survival, late complications affecting quality of life have been observed including short stature and endocrine dysfunction.[1-4] Reduced adult height in survivors is caused mainly by three factors: growth hormone deficit, early puberty, and impaired spinal growth.[1] All of these factors can be induced by CSI. Therefore, this study was conducted to compare height standard deviation score (SDS) at start of radiation therapy and at the last follow-up in children with brain tumor treated with CSI.

MATERIALS AND METHODS

Patient selection

All children diagnosed with brain tumor treated with 3D conformal radiation therapy (3DCRT) for CSI at Division of Radiation Oncology, Department of Radiology,

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Faculty of Medicine Siriraj Hospital between 2006 and 2014 were identified via the radiation oncology database for retrospective analysis after institutional review board approval (Si 606/2016). Inclusion criteria were as follows: (1) histological confirmed embryonal tumors or germ cell tumors (2) age > 3 years and ≤ 15 years at start radiation therapy (3) receiving craniospinal radiation therapy via 3-DCRT. Patients who have been followed-up less than 2 years and/or no weight and height measuring before start radiation therapy and once a year during follow-up were excluded.

Radiotherapy

Prescribed dose and target volumes for craniospinal radiation therapy and boost volume were obtained from patient chart and the online patient database.

Planning and evaluation

The dose-volume histograms (DVH) of the treatment targets and normal structures were evaluated from computer based planning system.

Follow-up

Assessments for weight and height measurement before and after completion of radiation therapy were obtained from patient chart and the online patient database.

Outcome variable and assessment

The primary endpoint for this study was height SDS at the last follow-up. Height SDS was calculated with age-matched mean value in the normal Thai population, and evaluated with INMU-Nutri Stat software program. Height SDS was categorized according to INMU-NutriStat software program, as follows: SDS < -2 SD corresponds to short stature, SDS between -1.5 SD to -2 SD corresponds to relatively short stature, SDS between -1.5 SD to 1.5 SD corresponds to normal stature, SDS between 1.5 SD to 2 SD corresponds to relatively tall stature, and SDS > 2 SD corresponds to tall stature. Loss of height was the difference between the initial height SDS (height SDS before start radiation therapy) and the latest height SDS (height SDS at the last follow-up).

Statistical analysis

All analyses were performed using STATA version 14.2. Data were presented by descriptive methods (frequency, percentage, mean ± SD). In addition, the independent-sample t-test and Mann-Whitney *U* test were used to compare the latest height SDS to the initial height SDS. Multivariable linear regression analysis was performed to evaluate the effect of potential risk factors on the latest height. All statistical analyses were two-sided with significance defined as a *P*-value < 0.05.

RESULTS

Patient demographics

Patient demographics and clinical information are shown in Table 1. Thirty four patients were included. Thirteen patients were excluded due to incomplete data or less than 2 years available follow-up data. Mean age at start of radiation therapy was 10.11 ± 3.68 years. Embryonal tumors were classified into two groups; average and high risk groups. The average risk group included patients with all of the following characteristics; were aged ≥ 3 years at diagnosis, had M0 disease, and underwent gross total tumor removal (GTR). Other patients and patient with sPNET were categorized as being in the high risk group.

Growth height

The data for each patient is detailed in Table 2. The mean initial height SDS was 0.09 ± 1.3. The mean latest height SDS was -1.15 ± 1.30. There were 4 patients (19%) with the latest height SDS < -2 and 8 patients (38.1%) with the latest height SDS < -1.5. Overall, the latest height SDS was significantly reduced. Mean loss of height SDS was 1.24 ± 1.08 (P < 0.001).

Three patients (14.3%) received growth hormone replacement therapy (GHRT). All who received GHRT have the latest height SDS > -2 (Table 3).

Multivariable risk factor analysis

The potential risk factors include sex, age at start radiation therapy, initial height SDS, vertebral mean dose, and hypothalamic-pituitary axis (HPA) mean dose. Linear regression analysis showed significant effect of initial height SDS and HPA mean dose on the latest height (Table 4). Their relations were shown in Figs 1 and 2. Patients with HPA mean dose more than 47Gy trended to have the latest height SDS less than -1.5 (Fig 2).

DISCUSSION

Decrease in the final height in children treated with radiation therapy has been observed for a long time, especially in children treated with cranial irradiation or craniospinal irradiation.[5-14] In our study, all children were treated CSI with 3D-CRT. The results were similar to recent data from Japan, using conventional radiation therapy and 3D-CRT. Odagiri K et al., found that 35% of children treated with CSI have the latest height SDS less than -2. In their study, 4 children had failure to

TABLE 1. Demographic and clinical information.

Diagnosis	Patient No.	Sex	Primary site	M stage	Extent of surgery	Age at start RT (years)	CSI dose (Gy)	Boost dose (Gy)
sPNET	1	F	S	M0	GTR	4.67	23.3	54
MB (average risk)	2	F	I	M0	GTR	8.92	23.4	54
	3	M	I	M0	GTR	9.5	23.4	54
	4	F	I	M0	GTR	10.83	36	55.8
	5	M	I	M0	GTR	4.08	30.6	50.4
MB (high risk)	6	M	I	M1	STR	13.5	36	55.8
	7	M	I	M4	GTR	7.92	36	55.8
	8	M	I	M1	STR	12	23.4	54
	9	F	I	M4	GTR	3.33	36	54
	10	M	I	M1	GTR	5.75	36	55.8
	11	M	I	M1	GTR	11.08	36	55.8
	12	F	I	M3	STR	5.33	36	55.8
Pure germinoma	13	M	P	-	Biopsy	14.08	36	54
	14	M	BG	-	Biopsy	13.67	21.6	36
NGGCT	15	M	BG	-	Biopsy	11.75	36	54
	16	M	P	-	Biopsy	13.42	24	36
	17	M	P	-	STR	14.08	40	54
	18	M	P	-	Biopsy	14.25	36	54
	19	M	SS	-	Biopsy	12.33	36	50.4
	20	M	SS	-	STR	8.5	36	54
	21	M	BG	-	STR	13.42	36	54

Abbreviations: sPNET=supratentorial primitive neuroectodermal tumor, MB=medulloblastoma, NGGCT=nongerminomatous germ cell tumors, F=female, M=male, S=supratentorial, I=infratentorial, P=pineal, BG=basal ganglia, SS=suprasellar, STR=subtotal tumor removal, GTR=gross total tumor removal, RT=radiation therapy, CSI=craniospinal irradiation

control disease, all of those children had the latest height SDS < -2. When these children were removed from the study group, only 15% of children had short stature. They also found that dose of CSI and age at start of RT has no effect on height or loss of height.[15]

Major causes of short stature in children treated with CSI are growth hormone deficiency, spinal bone growth arrest, and early puberty.[10,16-21] Cranial RT can induce the dysfunction of the HPA, resulting in disruption of growth hormone, followed by gonadal, adrenal, and thyroid hormones. These multiple hormone deficiencies lead to abnormal growth and puberty.[22] Furthermore, spinal irradiation has the additional effect on spinal bone growth. Shalet SM et al., found that spinal irradiation has a profound effect on spinal bone growth. The greater subsequent skeletal disproportion was associated with younger age at receiving CSI.[20]

More conformal radiation therapy technique in our study, 3D-CRT, has failed to reduce the incidence of short stature in children who have received CSI. The growth hormone deficiency (GHD) could develop even in those who received a dose as low as 10 Gy to the HPA.[22] The spinal growth retardation can be induced from CSI with a dose as low as 25 Gy.[23] Photon cannot avoid dose to HPA and vertebral bodies, so the late effect on height is still observed.

TABLE 2. Treatment related information and height.

Diagnosis	Patient No.	VB mean dose (Gy)	HPA mean dose (Gy)	GH	Age at the latest assessment (years)	Initial Height (SDS)	Latest height (SDS)
sPNET	1	36.2	37	No	8.75	0.12	0.02
MB (average risk)	2	24.7	26	No	12.75	0.22	-1.94
	3	24.1	24.3	No	12.25	-0.65	-1.39
	4	35	37	No	18.92	1.23	0.6
	5	29.8	30.5	Yes	12.5	-0.75	-1.84
MB (high risk)	6	37.2	38	No	16.58	2.83	1.18
	7	37.7	37.5	No	12.5	-1.03	-0.69
	8	22.8	24.3	No	17.5	0.18	-0.78
	9	37.1	37.4	No	5.75	0.41	-2.04
	10	37.8	38.7	Yes	11.83	0.22	0.16
	11	36.2	36.9	No	17.42	-1.65	-3.19
	12	34	37	Yes	13.5	1.15	-0.98
Pure germinoma	13	42.2	44.4	No	19.67	-0.4	-1.64
	14	21.1	35.6	No	19.83	0.12	-1.45
NGGCT	15	35.3	48.9	No	17.83	1.36	-1.92
	16	24.6	28.5	No	18.58	-1.15	0.21
	17	37.7	46.5	No	19.92	1.54	0.38
	18	34.8	36.7	No	16.17	-0.6	-1.33
	19	30.3	52.4	No	16	1.61	-1.06
	20	38.8	54.4	No	13.58	-2.73	-4.26
	21	35.1	50.8	No	18.58	-0.08	-2.09

Abbreviations: sPNET=supratentorial primitive neuroectodermal tumor, MB=medulloblastoma, NGGCT=nongerminomatous germ cell tumors,VB=vertebral bodies, HPA=hypothalamic-pituitary axis, GH=growth hormone replacement, SDS=standard deviation score

TABLE 3. Translation of height SDS in 3 patients treated with GHRT.

Patient no.	Height SDS (age)		
	At start RT	At start of GHRT	At the last assessment
5	-0.75 (4.08)	-2.48 (10.25)	-1.84 (12.5)
10	0.22 (5.75)	0.16 (11.83)	0.16 (11.83)
12	1.15 (5.33)	-0.93 (12.58)	-0.98 (13.5)

Abbreviations: GHRT=growth hormone replacement therapy, SDS=standard deviation score

TABLE 4. Multivariable linear regression analysis of risk factors for the latest height.

Risk factor	Coef.	(95% CI)	P-value
Sex	0.38	(-0.99 to 1.75)	0.56
Age at start RT	0.04	(-0.12 to 0.20)	0.57
Initial height SDS	0.72	(0.33 to 1.12)	0.001
VB mean dose	0.07	(-0.03 to 0.18)	0.14
HPA mean dose	-0.09	(-0.16 to -0.02)	0.02

Abbreviations: Coef.=Coefficient, CI=confidence interval, RT=radiation therapy, SDS=standard deviation score, VB=vertebral, HPA=hypothalamic-pituitary axis

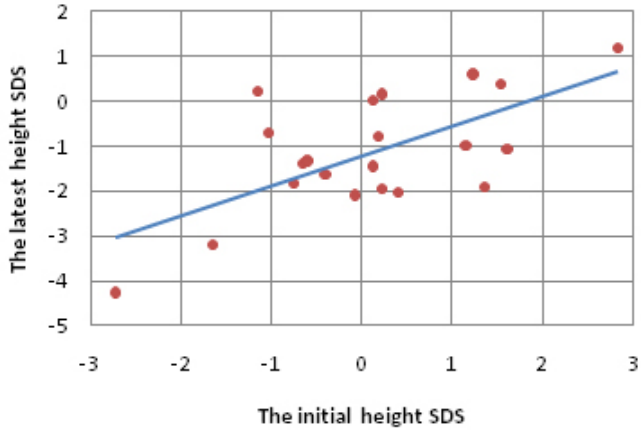


Fig 1. Scatter plot and the regression line (blue line) show positive relation between the initial height SDS and the latest height SDS.

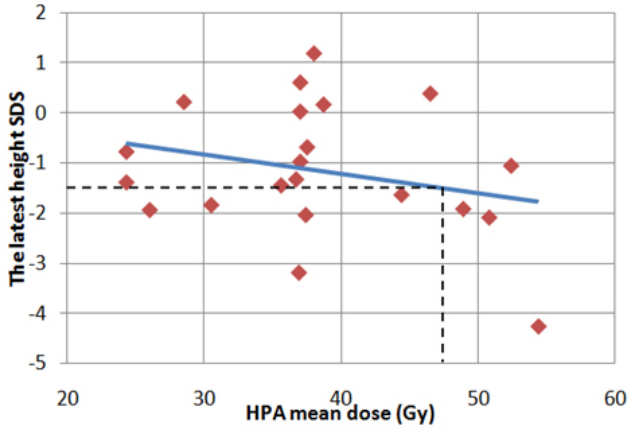


Fig 2. Scatter plot and the regression line (blue line) show negative relation between HPA mean dose (Gy) and the latest height SDS. HPA mean dose greater than 47 Gy is related to the latest height SDS less than -1.5.

Proton, the particle beam therapy which is highly precise to target and has rapid dose fall-off, has now published the role of limited dose to organs at risk to reduce radiation acute and late side effects including height. Eaton B.R. et al., found that children treated by CSI with proton achieve a greater height SDS than those with photon (-1.19 ± 1.22 vs. -2 ± 1.35) without significant difference in the incidence of GHD (53% vs. 57%).Their study also included whole vertebral bodies in CSI treatment volume, dose range 18-27 Gy. No dose to HPA was reported.[24]

In our exploratory analysis we found that the initial height and dose to HPA are related to the latest height. Dose to HPA greater than 47 Gy is associated with the latest height SDS less than -1.5. However, this observation is not strong enough to encourage the dose limitation to HPA due to the weak association. More supporting data is still needed.

Our study cannot evaluate the adult final height SDS because most children were aged under 18 years at the last follow-up. We only could report the latest height SDS. This major weakness was related to the retrospective nature of our study.

CONCLUSION

Children treated with CSI have significant loss of height even though 3D-CRT was used. The incidence of short stature is 19%. The initial height is strongly related to the latest height. Weak negative relation of dose to HPA related to the latest height was observed

Conflicts of Interest: The authors have declared no conflicts of interest.

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The Contamination of Intravenous Fluid by Felt-Tip Marking Pen Ink: A Pilot Study

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ABSTRACT

Objective: The practice of writing directly on infusion bags with felt-tip marking pen was suggested to cause contaminations. Recommendation against such practice has been published by manufacturers and health care authorities. A chromatography-based laboratory experiment was conducted to substantiate the possibility of ink constituents permeation through Polyvinylchloride (PVC) infusion bag.

Methods: A Viaflex® intravenous infusion bag was marked with a blue Artline® marking pen ink. Fluid samples were obtained at different time intervals and tested for any contaminations. A gas chromatography with mass spectrometry capability system was used to analyse fluid samples from infusion bag.

Results: Five fluid samples were obtained from the infusion bag at 0, 10, 30, 60, 120 minutes after ink exposure. Chromatograms from each sample were compared with a chromatogram from "blank" intravenous solution. There appeared to be no chromatographic evidence of ink constituents present in all intravenous fluid samples.

Conclusion: The practice of writing directly on Viaflex® infusion bags with a felt-tip marking pen has not resulted in contamination of intravenous fluid by ink constituents.

Keywords: Ink; marking pen ink; pilot study (Siriraj Med J 2018;70: 349-354)

INTRODUCTION

The practice of writing on plastic infusion bags for labelling purpose has been suggested to cause contaminations from chemicals in the ink. Several official statements and recommendations regarding the issues have been published and followed by healthcare providers.[1,2,3] Nevertheless, extensive literature review has not revealed any substantiated study which proved the statements to be true. However, the study of acute toxicity of marking pens on mice found: marking pen produced respiratory toxicity and neurobehavioral changes including abnormal posture and gait, tremors, falling, and/or hyperactivity, facial swelling, severe lacrimation and gasping.[4] Two previous studies could not demonstrate penetrations of ink chemicals through infusion bags, though limited by studies' design.[5,6] As abandoned by many practicing healthcare providers as a routine practice, writing directly on infusion bags might come to benefit in managing fluid and drug administration in emergency situations or in mass casualties.

The purpose of this study is to conduct a chromatography-based experiment to prove whether or not the plastic (PVC) infusion bags are permeable to chemicals from felt-tip marking-pen inks and cause contaminations.

MATERIALS AND METHODS

Study was conducted at the Toxicology laboratory located in Siriraj Hospital, Mahidol University, Thailand. Gas chromatography system with mass spectrometry

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capability (GC-MS) (Agilent® 7890A, Agilent Technologise, Inc., California, USA) was used for analysis.

ArtLine® felt-tip (Artlink Co., Ltd., Wangthonglang, Bangkok)marking pens, commonly used in the department of Anesthesia and more chemicals than other brands, were chosen for the study. A 99.99% HPLC-grade methanol and 99.9% purified NaCl were used in sample preparation. Specific infusion containers analysed were 250 ml Baxter® Viaflex 0.9% Sodium chloride intravenous fluid bag .The bag is 0.031 mm thick, composition and concentration of Na + 154 mmol/L and Cl- 154 mmol/L, total osmolarity is 308 mOsmol / L and pH 4.5-7. The Baxter® Viaflex, a type of specially formulated polyvinyl chloride (PL 146 plastic) that is widely used in intravenous solution container products, might have permeability to moisture and can interact with solutions to cause contaminations.[1,7,8]

GC-MS setup and reference solution preparation

Blue ArtLine® felt-tip marking pen ink was painted on Baxter® Viaflex 0.9% Sodium chloride bag to cover an area of 1 cm (width)*1 cm (length). The ink-covered area was cut and then soaked in 1 ml of 99.99% methanol to prepare a stock solution with a concentration of 100 unit (cm^3/ml); a 100 unit concentration stock solution merely contained the amount of ink possibly be painted in one layer to cover a one centimetre area. This stock solution was; intended to use for calibrating and standardising the analysis process, not for comparing or measuring as amount of ink. The stock solution was preserved in -20°C and sequentially diluted to 10, 5, 1 and 0.1 unit%. The stock and dilute solutions were incubated in 80°C and extracted by solid phase micro extraction technique (SPME fiber: divinylbenzene / Carboxen/ PDMS, Supelco®). Samples were injected into GC-MS system, and chromatograms were obtained from each sample of different concentrations.

The extraction and analysis of samples were carried out with CTC combi AAL auto sampler equipped with agitator and needle heater (for fiber conditioning and inter – extraction clean up coupled to a GC-MS (Agilent Technologics 7890A system)) and operated in the split/ splitless mode at an injection temperature of 250°C. The separation of target analytes were achieved on a DB-WAX fused capillary column 30 m x 0.25 mm i.d. x 0.25 µm film thickness. Helium (carrier gas) was set to a constant flow rate of 1 ml/min with linear velocity of 40 cm/s. The GC column oven temperature program was set as follows. Initially set at 40°C for 3 min, ramped at 10°C/min to 100°C, then ramped to 250°C at 25°C/ min, and held for 5 min. The MS operation condition includes transferline of 250°C, ion source of 230°C. electron ionization (EI) of 70 eV.

Although not the study's objective; chromatograms were compared with standard database (NIST Library and FT5 library) for identification of ink chemical constituents. Chromatograms from 100, 10, 5, 1 and 0.1 unit solutions showed identical patterns, which implied that the GC-MS analyses were consistently sensitive and accurate within the concentration range. Any amount of ink constituents found within the range of 0.1 to 100 unit concentrations would be accurately reported.

Chromatograms obtained from 0.9% Sodium chloride "blank" solution (250 ml Baxter® Viaflex bag) and from 0.1 unit% solution were used as references to compare with study samples.

Study samples preparation and analysis

Six samples of 250 ml Baxter® Viaflex 0.9% Sodium chloride bag was painted with Blue ArtLine® felt-tip marking pen ink in one layer to cover a 5 cm* 10 cm area. (Fig 1). If the bag allowed total penetration of ink constituents into the solution, it would result in a 0.2 unit (cm^3/ml) solution. Sample solution (5 ml) was aspirated immediately through aspiration port after the infusion bag was exposed to the blue ink, and 5-ml samples were aspirated on intervals of 10, 30, 60 and 120 min of exposure time.

Solutions aspirated from the bag were incubated in 80°C, followed by micro extraction technique using same SPME fiber.

If ink constituents were present in the solutions, it would be extracted into the fibers and detected by GC-MS.



Fig 1. Felt-tip pen ink covered Viaflex bag.

RESULTS

A reference chromatogram from 0.1 unit% solution consisted of 62 peaks, which represent 62 different constituents found in the blue Artline felt-tip pen. NIST and FT5 data base analysis could identify some, but not all the constituents (Fig 2).

Five fluid samples aspirated from different time intervals (0, 10, 30, 60 and 120 min) were analysed with GC-MS and were compared with the chromatogram from 0.9% "blank" sodium chloride solution (Fig 3).

The results showed identical chromatographic patterns of each sample from different time intervals, and they were identical to "blank" 0.9% sodium chloride solution (Fig 4).

There appeared to be no chromatographic evidence of contamination from exposing the bag to blue Artline felt-tip marking pen at 0, 10, 30, 60 and 120 min exposure time.

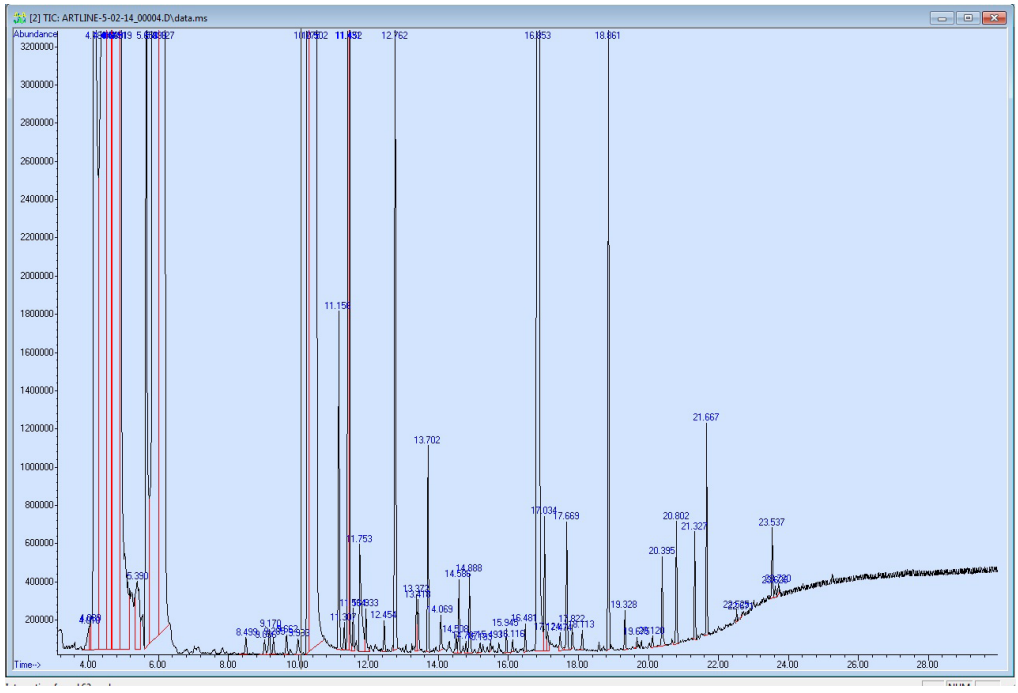


Fig 2. Chromatogram from reference sample.

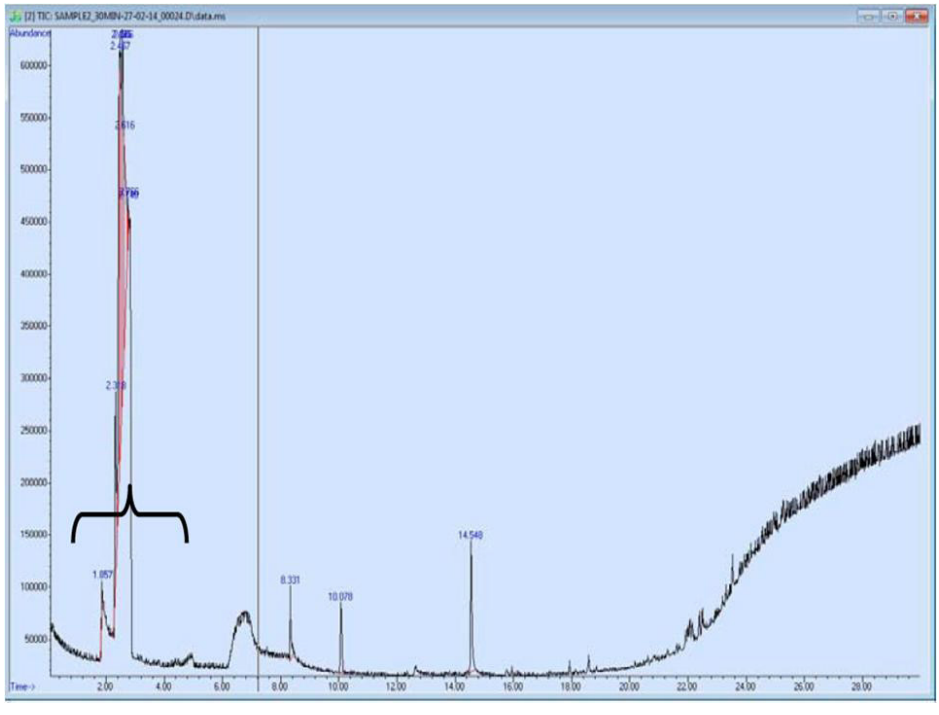


Fig 3. Chromatogram from "blank".

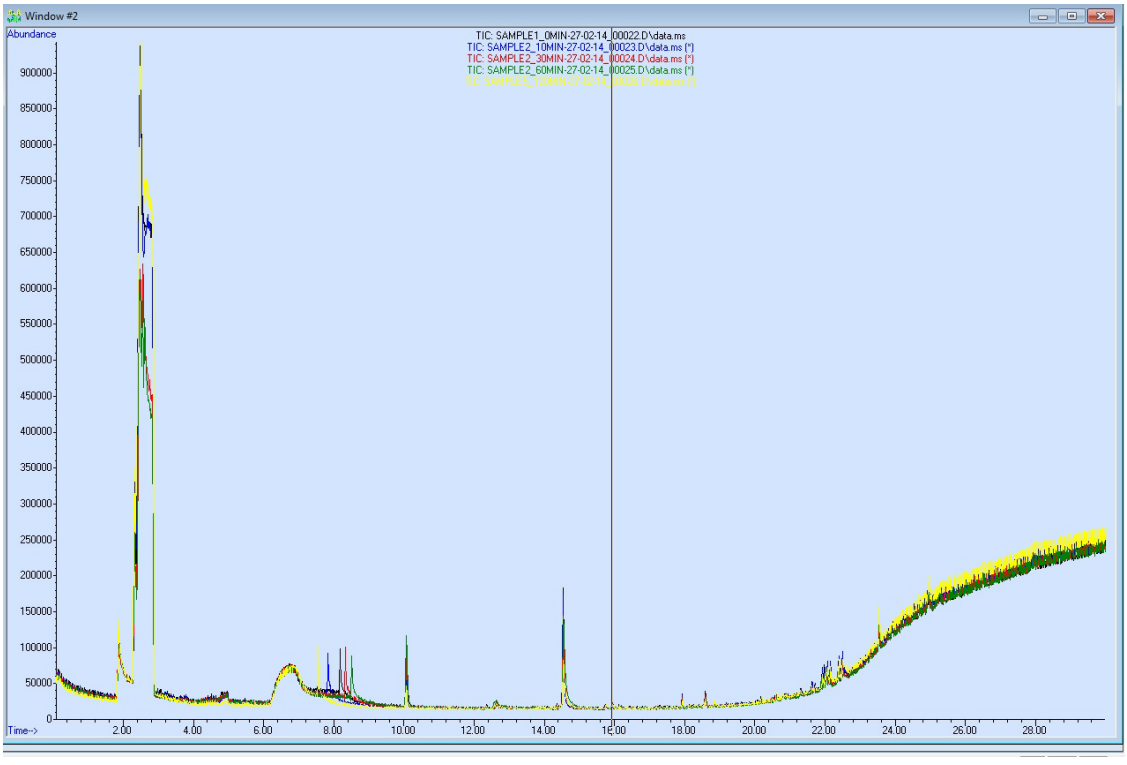


Fig 4. Comparison of chromatograms from different time intervals.

DISCUSSION

The purpose of the present study was to indicate whether the practice of writing directly onto PVC intravenous containers with felt-tip marking pen would cause contaminations from ink constituents.

The Viaflex bag used in the experiment was manufactured from the Baxter formulation of polyvinylchloride (PVC) known as PL146 Plastic. PVCs might have permeability to constituents used in felt-tip marking pen ink such as alcohol compound solvents.

Previous studies and recommendations were based on the hypothesis that alcohol compound or volatile substances in marking pen inks are permeable to the PVCs containers. The present study was the first to use highly sensitive GC-MS analysis to prove the hypothesis. List of ink constituents are shown in Table 1.

Limitations to our study include limited number of intravenous fluid containers and felt-tip marking pen. The types of container and pen were conveniently chosen as they are generally used in Siriraj Hospital's Department of Anesthesiology.

Although GC-MS analysis is one of today's most sensitive test to identify substances, the accuracy depends largely on meticulous sample preparation process and standardised GC-MS setup.

The toxicology laboratory guaranteed results to be accurate within the range of standard sample preparation (100-0.1 unit). If the ink constituents are present in smaller amount than GC-MS setup, it would not be detected accurately. The sensitivity of GC-MS setup could be increased, but it was the authors' opinion that the chosen setup was sufficiently sensitive to prove the hypothesis.

The authors chose a 5 cm* 10 cm ink-covered area to be tested because it contained much larger amount of ink used in real-life practice. If the intravenous container was proven to be resistant from contaminations in the experiment, the container in real-life situation having exposed to much lesser amount of ink would likely to be resistant as well.

ACKNOWLEDGMENTS

The authors wish to thank Siriraj Poison Control Center, Faculty of Medicine Siriraj Hospital for laboratory setup and chromatographic analysis process.

Conflict of interest: No conflict of interest declared

Financial disclosure: No source of financial support

TABLE 1. Ink constituents analysed from database.

Ink constituents analysed from database							
No.peak	**Rt**	**Library**	**Result**	**No.peak**	**Rt**	**Library**	**Result**
1	4.009	FT5	No matches found	32	13.701	W9N11	Benzaldehyde diethylacetal
2	4.038	FT5	No matches found	33	14.069	W9N11	Silanediol, dimethyl
3	4.181	W9N11	Ethanol	34	14.509	FT5	No matches found
4	4.419	W9N11	Ethanol	35	14.586	FT5	No matches found
5	4.645	W9N11	Ethanol	36	14.789	FT5	No matches found
6	4.663	W9N11	Ethanol	37	14.890	FT5	Phenylacetamide
7	4.799	W9N11	Ethanol	38	15.193	W9N11	Acetic acid, phenylmethyl ester
8	4.918	W9N11	Ethanol	39	15.490	FT5	Pyrilamine
9	5.388	FT5	No matches found	40	15.942	FT5	No matches found
10	5.650	W9N11	1-Propanol	41	16.115	W9N11	Benzenemethanol
11	5.899	W9N11	1-Propanol	42	16.483	FT5	Carbamazepine-M (formyl-acridine)
12	6.125	FT5	No matches found	43	16.852	W9N11	Benzyl alcohol
13	8.498	FT5	Dichlorophene TMS	44	17.036	FT5	No matches found
14	9.033	FT5	No matches found	45	17.125	W9N11	Butylated Hydroxytoluene
15	9.170	FT5	Dimethadione	46	17.476	FT5	Carisoprodol
16	9.283	FT5	No matches found	47	17.666	W9N11	Cyclododecane
17	9.663	W9N11	Cyclohexanone	48	17.210	W9N11	2-tert-Butyl-4-5-dimethylphenol
18	9.996	FT5	No matches found	49	18.112	W9N11	phenol
19	10.279	FT5	No matches found	50	18.862	W9N11	Ethanone,1- (2,3,4-trimethylphenyl) 1-1 (2,3,4-trimethylpheyl) ethanone
20	10.502	FT5	No matches found	51	19.331	FT5	Cyclandelate TMS
21	11.156	FT5	No matches found	52	19.676	FT5	Meprobamate
22	11.304	FT5	No matches found	53	20.122	FT5	No matches found
23	11.429	FT5	No matches found	54	20.396	FT5	Phenylethylamine,Beta
24	11.453	FT5	No matches found	55	20.800	W9N11	Phenol,p-tert-butyl-phenonl
25	11.566	W9N11	Propanolic acid 2- (1-ethoxyethoxy)	56	21.329	FT5	No matches found
26	11.750	W9N11	Acetic acide	57	21.668	FT5	No matches found
27	11.935	FT5	Dichlorophene	58	22.524	FT5	No matches found
28	12.452	W9N11	1,2.,4-Methenoazulene,decahydro-1	59	22.673	W9N11	1,4,7,10,13,16-Hexaoxacyclooctadec
29	12.761	W9N11	Benzaldehyde	60	23.535	W9N11	Phenol,4- (1,1,1,3,3-tetramethylbutyl
30	13.373	W9N11	Junipene	61	23.624	FT5	No matches found
31	13.415	W9N11	Naphthalene,1,2,3,5,6,8,8a-octa hydro-18a-dimethyl-7-(1-methylethenyl)	62	23.719	FT5	No matches found

What is already known on this topic

The use of felt-tip marking pens to label PVC intravenous fluid containers has been prohibited by several healthcare authorities in concern of the contamination of ink substances into the intravenous fluid to be given to patients.

What this study adds

Highly sensitive gas chromatography and mass spectroscopy analysis could not detect the contamination of ink material when using felt-tip marking pens to label Viaflex® intravenous fluid bags.

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Ureterocystoplasty in a Girl with Bilateral Ureterovesical Junction Obstructions and Small Bladder Capacity: The First Case Report of Thailand

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ABSTRACT

Objective: Ureterocystoplasty is one of the treatment options for small bladder capacity with hydroureter. To the best of our knowledge, there was no report of a patient who underwent this procedure in Thailand.

Case presentation: A 4-year-old girl, who presented with obstructive anuria at birth was diagnosed with bilateral ureteropelvic junction obstruction and small bladder capacity. At the age of 2 years old, she underwent a teapot ureterocystoplasty with left to right transuretero-ureterostomy with right ureteral reimplantation. Postoperative complication was observed. The bladder capacity was evaluated and kidney ultrasonography was done during the follow up. There was no complication during the perioperative period. The bladder capacity was increased from 25 ml to 240 mL in 2 years postoperatively. Both kidneys also showed the decrease in degree of hydronephrosis.

Conclusion: Ureterocystoplasty is a favorable treatment option for the patients with small bladder capacity and marked hydroureter. The procedure itself is not difficult to perform. Moreover, there are no mucous related complications and metabolic disturbances.

Keywords: Ureterocystoplasty; ureter; bladder augmentation (Siriraj Med J 2018;70: 355-356)

INTRODUCTION

Bladder augmentation is a treatment option in management of neuropathic bladder and small bladder capacity from other causes, especially in congenital anomalies, for upper urinary tract preservation. Although many types of tissues can be used for augmentation, enterocystoplasty is still popular despite complications of metabolic disorders[1] and mucus production. Ureteral bladder augmentation is another favorable option due to its advantages of no mucus and metabolic abnormalities.[2]

CASE PRESENTATION

A 4 year old girl was born at a gestational age of 33 weeks from a Caesarean section performed for oligohydramnios and placenta previa totalis. On the first day, she had anuria and ultrasonography revealed bilateral hydroureteronephrosis due to bilateral ureterovesical junction obstruction shown in Fig 1. Percutaneous nephrostomy was performed, sparing both the dilated ureters for further reconstruction. Intraoperatively, extremely small bladder was noticed.

At the age of 2 years, her serum creatinine was 0.6 mg/dl and bladder capacity was 25 ml. MR urography (MRU) was performed to evaluate both ureters for technical selection such as using one or both ureters, using distal ureter or entire ureter. MRU also reported multiple cystic changes of renal parenchyma in both kidneys as shown in Fig 2. Teapot ureterocystoplasty

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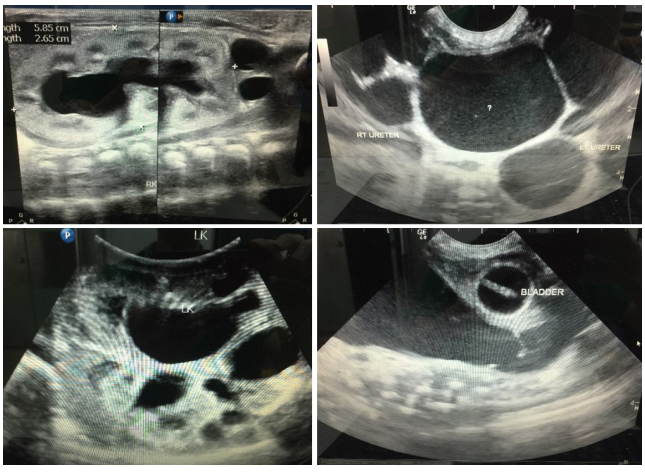


Fig 1. Ultrasonography 1 day after birth revealed bilateral UVJO.

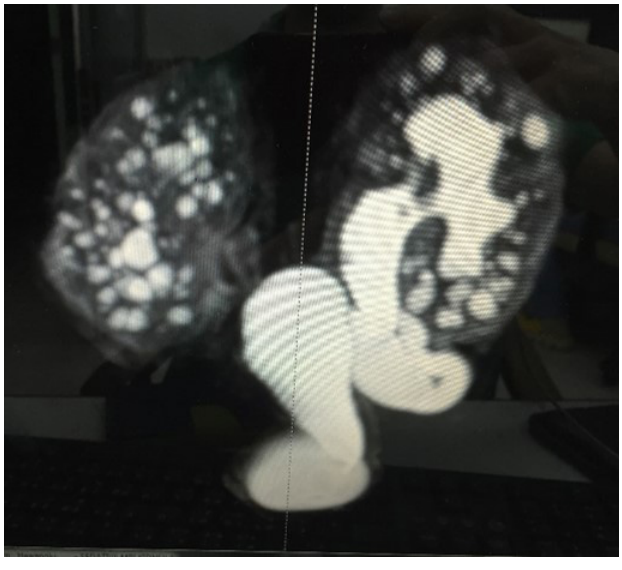


Fig 2. MRU revealed dilated ureters especially distal parts.

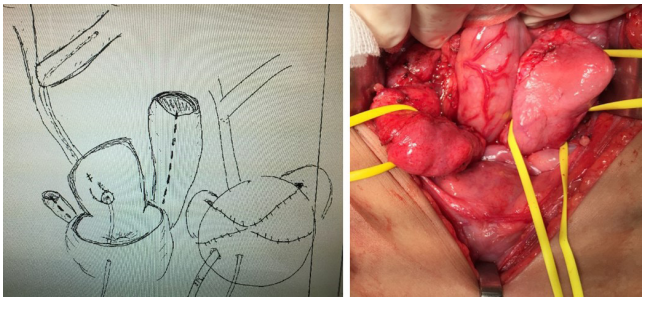


Fig 3. Ureteral bladder augmentation using both dilated distal ureters and transureteroureterostomy

was performed using both the dilated distal ureters as shown in Fig 3. Bladder was opened in coronal plane from the left to the right ureteric orifices and extended to detubularized both distal ureters, then both distal ureters were used as augmented tissue. Proximally, left to right transuretero - ureterostomy was done. Intraoperative bladder capacity after augmentation was increased to 70 ml. The postoperative period was uneventful and the patient was under regular follow up.

At 1 year follow up, she had spontaneous void of about 100 ml and on clean intermittent catheterization, she has residual urine of 140 ml. Her latest serum creatinine is 0.65 mg/dl. Follow-up ultrasonography has revealed decreased bilateral hydronephrosis.

DISCUSSION

Ureter is one of the best augmentation tissues for the bladder because it provides similar urothelial mucosa and muscular layer to bladder. There are no mucus related problems and metabolic complications. Some authors[2] have concluded that ureter can be used to improved storage function to the same extent as ileum. The improved bladder capacity after ureterocystoplasty can be more than two times.[3] There are different amounts of ureteral tissue available in each patient and that might be the only limitation for this procedure in non-dilated or small caliber ureter. The critical points of this procedure are case selection, the techniques that can be devised to obtain maximum amount of ureter and overall renal function.

The degree of dilatation of ureter and its extent should be evaluated preoperatively for reconstructive plan. Some authors[4], argue that there is no significant difference in bladder capacity when one or both ureters are used.

In the present case, we were successful in preserving both her kidneys and distal ends of both ureters were used for augmentation while proximally, left to right transureteroureterostomy was performed. The results were good, with improvement of hydronephrosis bilaterally as well as improvement in bladder capacity.

CONCLUSION

Ureteral bladder augmentation is a good alternative for improving storage function of small and poor compliant bladder compared to enterocystoplasty. For excellent outcome, this operation should be used in specific group of patients.

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Endoscopic Treatment of Bleeding Ileal Pseudo-diverticulum

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ABSTRACT

Objective: Jejunoileal bleeding is not common, with diverticular disease as the fourth common cause of gastrointestinal tract bleeding. However, the diagnosis is sometimes challenging and easily overlooked.

Case presentation: This is a case of a 71 years old lady presented with hematochezia. A bleeding ileal pseudodiverticulum was found and successfully controlled by endoscopic treatment.

Conclusion: Bleeding ileal pseudodiverticulum is an uncommon cause of lower gastrointestinal bleeding which can be treated endoscopically.

Keywords: Ileal pseudodiverticulum; lower gastrointestinal bleeding; endoscopic (Siriraj Med J 2018;70: 357-358)

INTRODUCTION

Diverticulum is the outpouching of mucosa of the hollow viscus organ, mostly in gastrointestinal tract. It is classified as, 'true diverticulum', in which the outpouching sac is covered by the whole layer of gastrointestinal wall, and, 'false or pseudodiverticulum', in which the outpouching sac is not covered by the whole layer. The latter is more common, and mostly encountered in the colon of elderly patients. Patients with diverticular disease usually are asymptomatic or might present with bleeding, infection or perforation.[1]

Although bleeding colonic diverticulum is the most common causes of lower gastrointestinal bleeding,[2] bleeding from ileal diverticulum is uncommon and might easily be overlooked. We present an uncommon case of lower gastrointestinal bleeding, in which the endoscopic treatment was successfully performed.

CASE PRESENTATION

A 71 years old woman with the underlying type 2 diabetes, hypertension, and dyslipidemia receiving clopidogrel 75 mg once daily as a prophylaxis for cardiovascular event presented to the hospital with hematochezia. Her vital signs were normal and initial examinations revealed a low hemoglobin level of 9.6 mg/dl. Other laboratory examinations were remarkable. Emergent colonoscopy (PCF H190, Olympus Medical System, Tokyo, Japan) was performed after rapid colonic purge and a small diverticulum, 3 mm in size, located within 2 cm from the ileocecal valve was seen. Non-Meckel pseudodiverticulum was the most likely diagnosis due to the small size and the location just proximal to the ileocecal valve. Blood clot inside the diverticulum was removed (Fig 1a) and a visible vessel with blood oozing was seen (Fig 1b). Hemostatic clips (EZ clip HX-610-090L, Olympus Medical System, Tokyo, Japan) were applied across the mouth of the diverticulum and the bleeding stopped (Fig 1c). The patient did not experience any recurrent bleeding during several months of follow-up and her hemoglobin level has improved.

Review of literature

Small intestine diverticular is much less common than colonic diverticular. The most common and well-known congenital diverticulum of the small intestine is Meckel diverticulum which may cause lower gastrointestinal bleeding, obstruction, perforation, inflammation, or volvulus.[3] Other false diverticulum were found mostly in duodenum surrounding the ampulla, followed by the jejunum and the ileum, respectively.[4,5] Most cases of small intestine pseudodiverticulum were asymptomatic, but several reports of complications of both acute complication

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Fig 1. The blood clot within the terminal ileal diverticulum (A). After the clot was removed, a visible vessel with blood oozing was seen (B) and hemostatic clipping was performed and the bleeding was stopped (C).

(such as bleeding, perforation, and infection) and chronic (such as pain and malabsorption) have been published.[6]

Gastrointestinal bleeding from the jejunoileal area is uncommon, with diverticular disease as the fourth common cause of bleeding.[7] The diagnosis of this condition is more difficult than colonic diverticulosis due to limited accessibility to the lesions by routine endoscopy. The identification of bleeding jejunoileal pseudodiverticular diseases using wireless capsule endoscopy, contrast-enhanced computed tomography (CT), and CT angiography have been reported in several literatures.[8-10] Among the reports of bleeding ileal diverticulum, the most common cause is bleeding from Meckel's diverticulum. However, in this case, according to the location and the size, the diagnosis of pseudodiverticulum was more suggestive. Similar to the criteria for diagnosis of bleeding colonic diverticulum, retaining blood clot was seen in the pseudodiverticulum, which is the definite diagnostic criteria for the diverticular bleeding.[1] However, sometimes the bleeding point might be difficult to identify especially in cases with multiple diverticulum. In a case report of bleeding from multiple jejunal diverticulum the bleeding point could not be identified, so no intervention was provided and the bleeding stopped spontaneously.[8]

Treatment of bleeding in small intestinal diverticular in most literatures included both surgery and endoscopic treatment such as injection therapy, hemocliping and heater probe.[9-11] Endoscopic treatment in these case series were delivered through upper GI endoscopy for duodenal diverticular bleeding and double balloon enteroscopy in ileal bleeding.[10,11] In another series, after the bleeding point was identified, either by CT scan or angiography, exploratory laparotomy was performed.[9] However, most of these reports were case reports or small case series. In the author's opinion, the treatment options should be individualized according to the location of the diverticulum and severity of bleeding. In cases presented with GI bleeding, routine upper and lower endoscopies are usually performed and the endoscopic treatment could be applied if the lesion could be demonstrated. However, in those cases that the bleeding point could not be reached by routine endoscopic examination, treatment attempts should be made based on the same principle as obscure overt GI bleeding patients. Capsule enteroscopy, device assisted enteroscopy, or angiography should be considered as the first diagnostic modality which depends on the bleeding activity.[12] In this case, fortunately, the lesion was located very close to the ileocecal valve so the endoscopic procedure was possible.

In conclusion, the author reported a case of ileal pseudodiverticular bleeding, which was successfully stopped by endoscopic clipping.

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Type A Aortic Dissection in a Postpartum Woman with Undiagnosed Marfan Syndrome

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ABSTRACT

Objective: To describe perioperative management for type A aortic dissection in a postpartum woman with undiagnosed Marfan syndrome.

Case presentation: A 30-year-old G2P1 Thai female at 39 weeks of gestation with undiagnosed Marfan syndrome gave birth at Siriraj Hospital, Bangkok, Thailand. After delivery, she developed episodes of hypotension and right hemiparesis. She was diagnosed with Marfan syndrome by clinical features of severe myopia, aortic root diameter Z-score ≥ 2 and bonafide FBN1 mutation detected by genetic study. The imaging studies showed strong evidences of type A aortic dissection and she underwent uneventful ascending aortic replacement under general anesthesia with extracorporeal bypass. The perioperative management was described.

Conclusion: Hemodynamic instability and pregnancy-related physiologic changes are the key factors to be concerned for perioperative management. The collaboration among cardiac surgeon, cardiac anesthesiologist and perfusionist is of great importance.

Keywords: Aortic dissection; Marfan syndrome; pregnancy (Siriraj Med J 2018;70: 359-362)

INTRODUCTION

Marfan syndrome is an autosomal dominant disorder which primarily affects connective tissue of the body, and clinical manifestations result in the cardiovascular, skeletal, and ocular systems.[1,2] The diagnosis of this particular syndrome relies on revised Ghent nosology criteria includes aortic root aneurysm, ectopia lentis (dislocated lens), and FBN1 mutation. In the absence of any family history, the presence of the two features is sufficient for unequivocal diagnosis and in case of the absence of one of these two cardinal features, the presence of an FBN1 mutation of positive systemic score is required. Stanford type A aortic dissection is a severely life-threatening condition in Marfan syndrome and is considered definitely for surgical treatment. It has been documented that the mortality is extremely high during the first 48 hours.[3] The risk of aortic dissection or dilatation dramatically increases during and after pregnancy in patients with Marfan syndrome due to imposition of the hyperdynamic and hypervolemic states.[2] However, there are several disorders that can cause acute aortic dissection in postpartum woman such as familial thoracic aortic aneurysm, Ehlers-Danlos syndrome-vascular type or arterial tortuosity syndrome. The following case profiles the uncommon case of a 30-year-old undiagnosed-Marfan-syndrome woman with Stanford type A aortic dissection in a postpartum period. In accordance with our institutional guidelines, the patient gave written informed consent for the publication of this report.

CASE PRESENTATION

A 30-year-old Thai female, G2P1, in the 39th week of pregnancy had an uneventful vaginal delivery. She developed an episode of hypotension after undergoing tubal sterilization under local anesthesia and she underwent emergency exploratory laparotomy under general anesthesia due to suspicious of intraperitoneal bleeding. Unfortunately, it was negative finding and

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explained causes of hypotension were not detected. Six hours later, she developed motor aphasia and right hemiparesis and her physical examination showed diastolic murmur grade III of VI at right parasternal border. Transthoracic echocardiogram revealed aortic root dilatation (4.3 cm in diameter) with moderate aortic insufficiency and intimal flap in ascending aorta. CT of her brain strongly suggested left middle cerebral artery territory infarction and CTA of thoracic aorta showed Stanford A aortic dissection involving brachiocephalic trunk, along left common carotid artery, proximal left subclavian artery, proximal part of celiac trunk and superior mesenteric artery without evidence of rupture of aortic dissection. She was scheduled for emergency ascending aortic replacement.



Fig 1. Transesophageal echocardiography showed the intimal flap in the ascending aorta.



Fig 2. Thoracic CTA showed dilated ascending aorta with intimal flap.

In the operating room, the patient was placed supine and standard monitoring (electrocardiography, noninvasive blood pressure, and pulse oximetry) was established. The right radial artery was cannulated for continuous invasive blood pressure monitoring under local infiltration of 2% lidocaine 0.5 mL and the large-bored peripheral lines were placed. After three minutes of denitrogenation with 100% oxygen, midazolam 8 mg, fentanyl 200 µg, and rocuronium 50 mg were injected, tracheal intubation was uneventfully accomplished and general anesthesia was maintained with isoflurane (1% end-tidal in 60% oxygen). After induction of anesthesia, a 7 F double-lumen catheter and a 8 F introducer sheath were placed in the right internal jugular vein for administration of medication and fluids and central venous pressure monitoring. Transesophageal echocardiographic probe was inserted for evaluating severity and the entry site of aortic dissection and cardiac morphology and function were assessed.

The patient's chest, abdomen, and groins were prepped and draped under aseptic fashion, median sternotomy and the right groin incision were performed and 15,000 units of heparin were administered via central venous line. The extracorporeal system was established by cannulation of the right femoral artery for arterial pump flow and cannulation of the right atrium for venous drainage. Distal ascending aorta was cross-clamped, ascending aorta was opened and blood cardioplegia was directly given via both coronary artery ostiums. The cardiac surgeons performed an ascending aortic replacement with Gelweave graft no.24 and aortic valve commissural resuspension under moderate hypothermia (28 °C). During extracorporeal bypass, mean arterial pressure (MAP) averaged 40 mmHg with 3-5 L/min of cardiac output and norepinephrine was continuously administered to maintain MAP over 60 mmHg. The period of time on cardiopulmonary bypass was 121 minutes and aortic cross-clamped time was 87 minutes. After rewarming the patient, discontinuaton from extracorporeal bypass was uneventful with stable hemodynamics.

Reversal of heparin effect was by administering 15,000 units of protamine and the first activated clotting time was prolonged (167 seconds) after protamine administration. The patient was transfused 2 units of packed red blood cells, 5 units of fresh frozen plasma, 5 units of platelet concentration and 5 units of cryoprecipitate for optimizing coagulation, the patient was transferred to the cardiothoracic intensive care unit in the hemodynamically stable condition. After 10 hours of postoperative mechanical ventilation, the patient was successfully extubated. Neurological symptom and sign were evaluated and motor power of

the right-side was slightly increased with grade III of V. She was transferred to the general postpartum ward and was treated in rehabilitation program. Genetics medicine was consulted for evaluation and assessment of Marfan syndrome, and direct DNA sequencing of both DNA strands was performed for mutation detection in the entire coding sequences (exon 2-66; which consists of 66 fragments) for FBN1 gene, and FBN1 NM_000138.4:C.6658C>T[p.Arg2220Term] was identified in this patient. She was given β-blocker. She was discharged on the 14th postoperative day.

DISCUSSION

Aortic aneurysm or aortic dissection uncommonly occurs in young women, but it can occur. It is usually associated with pregnancy with the most incidence of aortic dissection in the third trimester caused by hyperdynamic and hypervolemic state of pregnancy and inhibition of elastin and collagen deposition by estrogen and relaxin.[4] In this case, the onset of aortic dissection was in the early postpartum period. Aggravating factors of aortic dissection in this case possibly were multifactorial such as the effects of pregnancy, pathophysiologic changes of Marfan syndrome, and hemodynamic changes in heart rate, systemic blood pressure, and systemic vascular resistance (vaginal delivery, tubal sterilization, exploratory laparotomy). Based on the revised Ghent nosology criteria, Marfan syndrome can be diagnosed by just cardinal cardiovascular manifestation plus Bonafide FBN1 mutation. Therefore, the patient might have been underdiagnosed due to subclinical physical appearance (myopia, high-arched palate) and the absence of familial history or this was due to unawareness of her clinical features. If this case was diagnosed before or during pregnancy, antenatal care strategy to prevent aortic dissection such as frequent echocardiography monitoring every 3 months and taking β-blocker would be necessary. Vaginal delivery with epidural analgesia can be performed safely and cesarean section also be performed under general anesthesia and regional anesthesia. Marfan syndrome is an autosomal dominant disorder, and her children might be affected, so genetic study should be done during childhood period. β-blocker is a beneficial medication to prevent cardiovascular sequelae from Marfan.

For the anesthetic consideration, the difficult airway can be suspected due to the airway mucosal edema and narrow airway passage (gestation hormonal effects) and Marfan manifestation (high arched palate). Smaller endotracheal tube, stylet, and video laryngoscope should be prepared. This patient was successfully intubated without any complications with McCoy blade laryngoscope no.4. Hypertension and tachycardia must be avoided, so high dose of opioids, lidocaine and β-blocker can attenuate hemodynamic changes during laryngoscopy and intubation. Ruptured aortic dissection is the lethal complication, so cardiac surgeons, perfusion and extracorporeal circuit should standby in the operating room in case of hemodynamic collapse after induction and intubation. During on cardiopulmonary bypass with moderate hypothermia, adequate organ perfusion should be optimized by adequate pump flow 3-5 L/min maintaining mean arterial pressure 50-60 mmHg. However, this patient's MAP was continuously lower than 50 mmHg (40mmHg) even with full pump flow. The low MAP in this patient might be caused by physiologic anemia and hemodilution (pregnancy physiology) and vasodilatation from progesterone effect on vascular tone. Progesterone might play a role on vascular integrity and permeability promoting decreased systemic vascular resistance and interstitial edema, and progesterone effect might last 6-8 weeks after placental delivery.[5] Norepinephrine is drug of choice to counter severe vasodilatation phenomenon during extracorporeal bypass, so 0.05-0.1 μg/kg/min of norepinephrine was continuously infused to maintain MAP 50-60 mmHg in this patient.

Coagulopathy commonly occurs after prolonged extracorporeal circulation, continuous bleeding, residual heparin effect, and hypothermia. A hypercoagulable state is usually present in the third trimester of pregnancy and late postpartum,[6,7] but there was no significant effect in this case. Therefore, the patient was treated coagulopathy as a non-pregnant patient, adequate heparinization reversal, appropriate quantity of fresh frozen plasma and coagulation factors replacement, for maintaining normothermia and coagulation test are the important keys to correct coagulopathy. Fortunately, there was no massive bleeding from vagina and the previous surgical wound, and coagulation test showed no abnormality.

CONCLUSION

Subclinical features and the absence of familial history are the difficult points for definite diagnosis of Marfan syndrome. Acute aortic dissection Stanford type A in pregnancy is rare and difficulty to diagnose. Transthoracic echocardiography is a first-line useful technique for diagnosis and detection of severity and consequences of aortic dissection and computerized tomography of aorta is definitely a tool to detect origin of dissecting flap and the extension of dissection. Hemodynamic instability, pregnancy-hormonal effect and coagulopathy are the important keys for safe perioperative management during aortic surgery and extracorporeal bypass.

ACKNOWLEDGMENTS

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Leishmaniasis: An Evolving Public Health Concern in Thailand

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ABSTRACT

Leishmaniasis is a parasitic disease caused by flagellated protozoa of the genus *Leishmania*. It is transmitted by the bite of an infected sandfly. The 3 main clinical forms of the disease are cutaneous leishmaniasis (CL), visceral leishmaniasis (VL) and mucocutaneous leishmaniasis (MCL). Prior to 1996, all leishmaniasis cases were infected during the visit to the endemic areas. Thereafter, autochthonous leishmaniasis cases have been reported in Thailand. From 1996 to the present, at least 21 cases of autochthonous leishmaniasis have been confirmed in Thailand. *Leishmania siamensis*, a novel species of *Leishmania*, was suspected of being the causative pathogens in some of those cases, However, the data supporting the existence of this new species is limited. Until recently, in-depth investigation using molecular characterization and isoenzyme analysis revealed that this suspected novel species consists of 2 different, but closely related strains: *L. siamensis* and *L. martiniquensis*. *L. martiniquensis*, a rare species firstly discovered on Martinique Island, is the cause of leishmaniasis in the majority of cases. Meanwhile, *L. siamensis*, a true novel species firstly and only reported from Thailand, was confirmed as the cause of leishmaniasis in two autochthonous cases. Two clinical forms (CL and VL) have been observed in both *L. martiniquensis* and *L. siamensis* infection. The DNA of *L. martiniquensis* was found in black rats, suggesting their role as a natural reservoir. The presence of *L. martiniquensis* DNA in two sandfly species (*Sergentomyia gemmea* and *Sergentomyia barraudi*) that are commonly found in affected areas may also suggest their role as potential vectors. Here, we update the status of leishmaniasis in Thailand and its emergence as a potential public health concern.

Keywords: Thailand, Southeast Asia; *Leishmania*, autochthonous leishmaniasis; *Leishmania. Siamensis; Leishmania martiniquensis* (Siriraj Med J 2018;70: 363-376)

INTRODUCTION

Leishmaniasis is one of the world neglected diseases caused by obligate intracellular flagellated protozoa in the genus *Leishmania*. It is transmitted by the bite of female Phlebotomine sandflies and over 90 species of this sandfly genus have been shown to transmit *Leishmania*. Approximately 20 species of *Leishmania* are capable of infecting humans.[1,2] This disease is primarily zoonotic which means that mammals such as rodents, hyrax and dogs are major natural reservoirs.[1,2] In some circumstances, this disease can also be anthroponotic which means humans are a major reservior.[1,2] Clinical presentations of leishmaniasis vary depending on host immunity and the involved *Leishmania* species. The 3 main clinical presentations of the disease are cutaneous (CL), visceral (VL) and mucocutaneous (MCL) leishmaniasis.

Leishmaniases are prevalent in more than 98 countries in the tropics, the subtropics and Mediterranean regions.[1] The disease is often classified as 'Old World' and 'New World', according to the regions of the world where it primarily occurs and the vector presence at those sites.[1,2] Old World defines endemic regions in the Eastern Hemisphere including Asia, Africa and southern Europe.[1,2] New World leishmaniasis occurs mainly in the Western Hemisphere, extending from central to south Texas and from Central America and South America.[1,2] Prior to

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1996, this disease was considered rare in Thailand and all reported cases were imported.[3,4] However, autochthonous leishmaniasis cases in patients with no history of travel outside Thailand have been reported since then.[5-25] Since 2005, a suspected novel species of *Leishmania*, proposed as *L. siamensis*, has been reported as a culprit pathogen in many autochthonous leishmaniasis cases in Thailand.[5,7,11-13,16-18] Those suspicious species were categorized into 2 lineages: TR and PG based on sequence polymorphisms of the ITS1, HSP70 and CYT B loci.[26] Recent data derived from thorough molecular genetic characterization and isoenzyme analysis confirmed that the 2 lineages are actually distinctive species. Specifically, lineage PG is *L. martiniquensis* and lineage TR is the true novel species *L. siamensis*. Both *L. martiniquensis* and *L. siamensis* have recently emerged in Thailand.[26,27] *L. martiniquensis*, is a species endemic to Martinique (an island overseas region of France that is located in the Caribbean sea), which was identified as the cause of the majority of autochthonous leishmaniasis cases in Thailand.[5,7,11-13,16,17,28,29] However, 2 known cases of autochthonous leishmaniasis cases were found to be caused by *L. siamensis*, a true novel *Leishmania* species first discovered in Thailand.[18,26,27]

The aim of this review was to update the status of leishmaniasis in Thailand and its emergence as a potential public health concern in Thailand. In this article, we focus on *L. martiniquensis* and *L. siamensis* relative to species characterization, clinical presentations and potential vectors as well as animal reservoirs. The retrospective data in this review was derived from published PubMed articles and from reports published by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand from 1996 until the present.

Classification and biology of *Leishmania*

Leishmania are an obligate intracellular flagellate protozoa in the family Trypanosomatidae, order Kinetoplastida, Genus *Leishmania*. *Leishmania* has recently been classified into 2 major phylogenetic lineages i.e., Euleishmania and Paraleishmania, based on thorough molecular data and isoenzyme characterization.[1,30] The lineage Euleishmania is divided into 3 subgenera (*Leishmania, Viannia and Sauroleishmania*) and 1 complex (*L. enrietii* complex).[30-32] A few articles proposed *L. enrietii* complex as an additional *Leishmania* subgenus, but this data remains inconclusive.[1,32-34] *Euleishmania* is a major pathogenic lineage that causes human leishmaniasis, in which subgenus *Leishmania* and *Viannia* are the most common groups that infect humans.[1] Subgenus *Leishmania* is the most common group that causes VL; while, subgenus *Viannia* can cause both VL and CL.[1,35] In contrast, *L. enrietti* complex mainly infects guinea pigs, and human infection is zoonotic and is considered rare.[1] Subgenus *Sauroleishmania* is a cause of leishmaniasis in lizards and no human infection has been reported.[1] The lineage *Paraleishmania* comprises 5 species, but only *L. colombiensis* was found to infect humans.[1] Transmission of *Leishmania* occurs when humans are bitten by female sandflies. In human stage, *Leishmania* motile promastigotes enter the human body at the bite site and are phagocytosed by resident macrophages, dendritic cells and neutrophils.[2] The promastigotes multiply intracellularly and then develop into aflagellate amastigotes. In case of CL and MCL, amastigotes are found in resident macrophages in the skin or mucocutaneous lesions. In cases of VL, amastigotes develop in phagocytes of the reticuloendothelial system including: liver, spleen and bone marrow causing hepatomegaly, splenomegaly and bone marrow suppression, respectively. The life cycle is then completed when sandflies receive parasitized cells containing amastigotes during blood feeding on infected human. Amastigotes then transform into promastigotes in the gut and further migrate to the proboscis of the sandfly. The infection cycle is then repeated when an infected sandfly feeds on a new uninfected human.

Species characterization of emerging Leishmania species: identification of *L.martiniquensis* and *L.Siamensis*

Leishmania species are indistinguishable based on their morphological appearance, so species discrimination requires molecular genetic identification and isoenzyme characterization.[1] A wide variety of genetic markers including small subunit ribosomal RNA (SSU-rRNA)[36], DNA polymerase a catalytic subunit (POLA)[37], RNA Polymerase II largest subunit (RPOIILS)[37], heat shock protein 70 (HSP 70)[38], internal transcribed spacer 1 (ITS1)[36,39,40] and cytochrome b (CYT B)[41] have been used for species identification and phylogenetic diversity determination of *Leishmania*. Comparison of SSU-rRNA gene sequence has been used to effectively distinguish phylogenetic relationships among the genera of Kinetoplastida. However, due to low interspecies variability within *Leishmania* spp., species discrimination based on SSU-rRNA gene sequence comparison is indecisive.[26] As such, other methods of genetic sequence analysis should be employed to facilitate decisive species taxonomic identification. Many studies have shown that multiple molecular sequence comparisons produce reliable data that is capable of resolving questions relating to *Leishmania* taxonomic and phylogenetic diversity.

In 2005, a novel species of *Leishmania* was suspected in an autochthonous leishmaniasis case that occurred in Phang Nga Province, Thailand, based on ITS1 and mini-exon rRNA sequence analysis.[17] Thereafter, many autochthonous leishmaniasis cases that were suspected of being caused by a new species of *Leishmania* were reported.[5,7,11,13,16,17] The baseline characteristics of autochthonous leishmaniasis cases reported from Thailand and Myanmar from 1996 onward are summarized in Table 1. The new suspected *Leishmania* species was proposed as *L. siamensis*, but at that time its taxonomy was still inconclusive. Lack of a conclusive determination regarding the given name and existence of this proposed new species was an ongoing source of confusion among scientists and clinicians. The ongoing confusion in the terminology of *L. siamensis* had occurred for a period of time. However, recent studies by *Leelayoova* et. al., shed light on taxonomic classification of this novel species.[26,27] In those studies, species identification was performed by phylogenetic analysis of 4 genetic loci (SSU-rRNA, ITS1, CYT B and HSP70) as well as by isoenzyme analysis.[26,27] In phylogenetic analysis, all suspected novel *Leishmania* species, previously reported as *L. siamensis* were grouped together in the same clade as other *Leishmania* species in the division *Euleishmania*, subgenus *Leishmania* based on their SSU-rRNA sequence.[26,27] Phylogenetic tree analysis using Neighbor Joining method is shown in Fig 1. SSU-rRNA sequences of all suspected novel *Leishmania* species were 100% identical as published previously.[26,27] Phylogenetic tree construction based on ITS1 region showed that most novel species reported were grouped into the same taxa as *L. martiniquensis*.[26,27] However, one strain previously reported as *L. siamensis* lineage TR formed a separate branch from the others which indicated a specific strain. (Fig 1A)[26,27] HSP70 gene also defined *L. siamensis* strain to be distinct from the others as published previously.[26,27] The data showed that only one reported strain was truly *L. siamensis (L. siamensis* lineage TR), but most of the other strains were actually *L. martiniquensis* based on genetic sequence analysis (Fig 1A&B). The novel *L. siamensis* (lineage TR) strain was found to be closely related to *L. enrietti* as shown in Fig 1B. The Genbank accession numbers and the names of both suspected and confirmed *Leishmania* species from reported studies are shown in Table 2. Isoenzyme analysis also confirmed the differences between those reported strains. A majority of those strains were in zymodeme MON-229, similar to *L. martiniquensis* reference strain.[26,27] In contrast, a true *L. siamensis* (previously *L. siamensis* lineage TR) was grouped in zymodeme MON-324 which is different from the isoenzyme profiles of *L. martiniquensis*.[26,27]

In summary, the presence of a new *Leishmania* species, namely *L. siamensis* was confirmed in Thailand. However, most of the suspected novel Leishmaniasis cases were caused by *L. martiniquensis*.

Reported autochthonous Leishmaniasis cases in Thailand

During 1960 to 1996, all reported leishmaniasis cases in Thailand were imported, with infections occurring during visits to endemic areas outside Thailand. The first autochthonous case of visceral leishmaniasis in Thailand, caused by an unknown *Leishmania* species, occurred in 1996, but was reported in the literature in 1999.[19] Since that time, sporadic cases of autochthonous leishmaniasis have been reported.[5-25] In 2005, a suspected new species of *Leishmania* was identified as a cause of autochthonous leishmaniasis in a man living in Phang Nga Province which is located in the South of Thailand.[17] Later, the causative species in that infection was confirmed to be *L. martiniquensis*.[26]

To date, at least 21 cases of autochthonous leishmaniasis have been reported from across Thailand.[5-20,23-25] All of those patients had no history of traveling abroad or visiting disease endemic areas. A majority of those patients lived in the southern region of Thailand at the time of their infection. Regions from which autochthonous leishmaniasis has been reported are shown in Fig 2. The mean age of these reported cases was 40.7±19.8 years (ranged: 3-81) and 13 (62%) and 8 (38%) cases were male and female, respectively. Twelve (57.1%), 5 (23.8%) and 4 (19%) cases lived in the southern, northern and central regions of Thailand, respectively. Ten (47.6%) patients had coinfection with HIV with a wide range of absolute CD4 cell count (range: <50 to 543 cells/mm^3. Sixteen out of 21 (76.2%) cases presented with visceral leishmaniasis, 4 (19%) cases had cutaneous leishmaniasis and 1 (4.8%) case was asymptomatic. Regarding the species that caused infection, 10 (47.6%) cases were infected with *L. martiniquensis*, 3 (14.3%) cases with *L. donovani*, 2 (9.5%) cases with *L. siamensis* and 1 (4.8%) case with *L. infantum* and 4 (23.8%) cases in which the species was unknown. Clinical presentations and baseline characteristics of reported autochthonous leishmaniasis cases are summarized in Table 1. In addition, 3 leishmaniasis cases from Myanmar that were visiting Thailand to seek medical care or to accompany family members were diagnosed with *L. martiniquensis* infection. Those patients were moved to Thailand before symptoms developed and they had no history of traveling outside Thailand or Myanmar. The baseline characteristics of reported Burmese cases are also included in Table 1.

TABLE 1. Baseline characteristics and clinical manifestations of autochthonous leishmaniasis cases reported in Thailand and Myanmar from 1996 to present. *Previously reported as L. siamensis or suspected new species, ¶Level post-treatment.

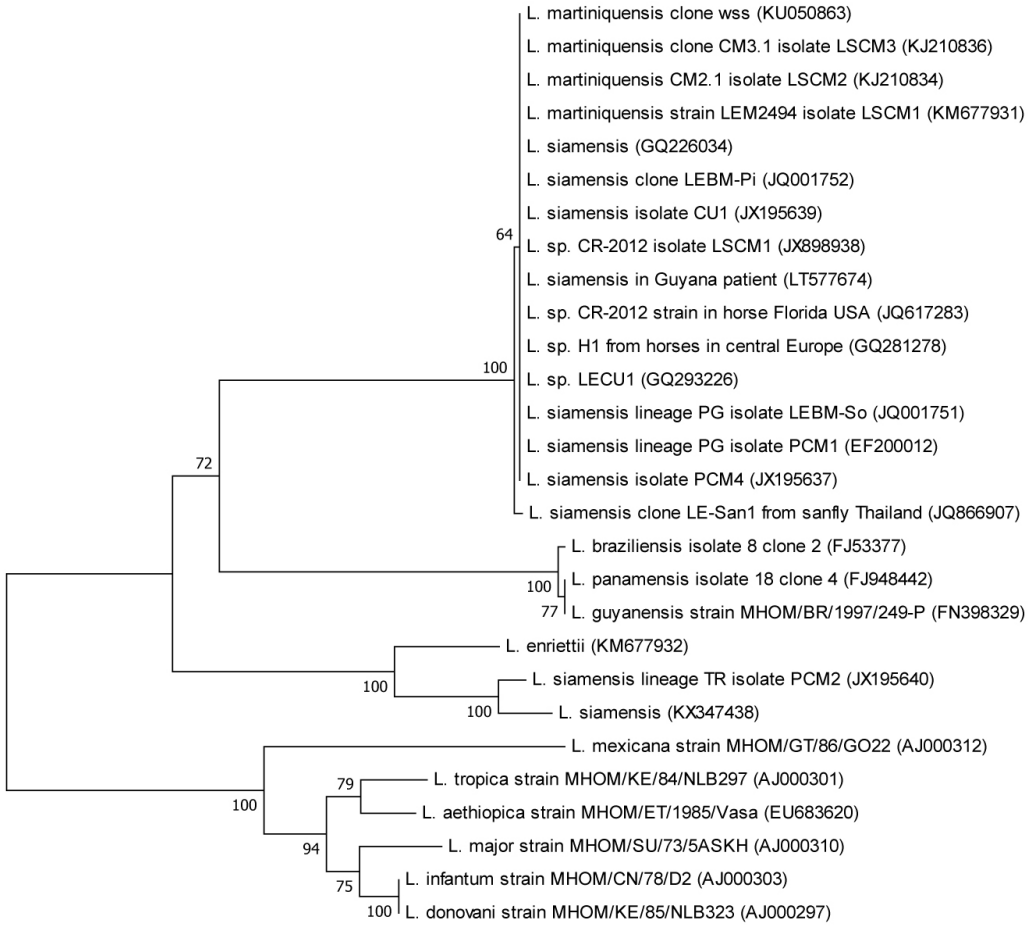
Case no.	Year	Location	Age (yr)	Sex	Occupation	HIV status (CD4 cells/mm^3)	Other underlying conditions	Clinical classification	Confirmed species	Laboratory investigation				References
										Microscopy (presence of amastigotes)	PCR positive in	Culture	DAT or IFA	
1	1996	Surat Thani	3	F	Student	Neg		VL	N/A	BM	BM	N/A	IFA 1:16,384	19, 20, 21
2	2005	Nan	40	M	Construction worker	Neg	Amphetamine, alcohol, and opium addict	VL	*L. donovani*	BM, skin nodule biopsy	BM	N/A	N/A	20, 21, 25
3	2005	Phang Nga	55	M	Rubber planter	Neg	-	VL	*L. martiniquensis**	BM	BM, blood	N/A	DAT 1:200¶	17, 20, 21
4	2006	Songkla	62	F	N/A	Neg	AIHA	VL	N/A	BM	N/A	N/A	N/A	20
5	2007	Nakhon Si Thammarat	44	M	Rubber planter	Neg	DM type 2 with retinopathy	VL	*L. donovani*	BM, LN	BM	N/A	N/A	20, 21
6	2007	Songkla	81	M	Shaman	Pos	-	VL	*L. donovani*	BM	BM	N/A	N/A	20, 21
7	2007	Bangkok	66	M	Retired officer	Neg	DM type 2, HT	VL	*L. infantum*	BM	BM	N/A	DAT 1:3,200	9, 20, 21
8	2008	Chaing Rai	45	M	Laborer	Pos (<50)	-	VL, DCL	*L. martiniquensis**	Skin biopsy	Skin biopsy, blood, saliva	Blood -, skin biopsy -, saliva -. and urine -	N/A	13
9	2008	Chantaburi	37	M	Fisherman	Pos (129)	TB, HCV, IVDU	VL	*L. martiniquensis**	BM, kidney biopsy	BM, kidney biopsy		DAT >1:1,600	16, 21
10	2008	Songkla	52	F	N/A	N/A	-	CL	N/A	Skin lesion	N/A	N/A	N/A	20
11	2009	Songkla	46	M	Rubber planter	Pos (175)	Evans syndrome	VL, CL	*L. martiniquensis**	BM, LN, blood smear	BM, LN, blood, buffy coat, saliva, urine	BM +, blood +, ulcer discharge -	N/A	7, 12, 13, 15, 20
12	2010	Satun	5	F	Student	Neg	β-thalassemia trait	VL	*L. martiniquensis**	BM, liver	BM, liver	N/A	DAT 1:3,200	11, 20

Abbreviations: HIV, human immunodeficiency virus; PCR, polymerase chain reaction; DAT, direct agglutination test; IFA, indirect immunofluorescence assay; N/A, not available; AIHA, autoimmune hemolytic anemia; DM type 2, diabetes mellitus type 2; HT, hypertension; TB, tuberculosis; HCV, hepatitis C virus; IVDU, intravenous drug use; PCP, pneumocystis carinii pneumonia; VL, visceral leishmaniasis; DCL, diffuse cutaneous leishmaniasis; CL, cutaneous leishmaniasis; BM, bone marrow; LN, lymph node

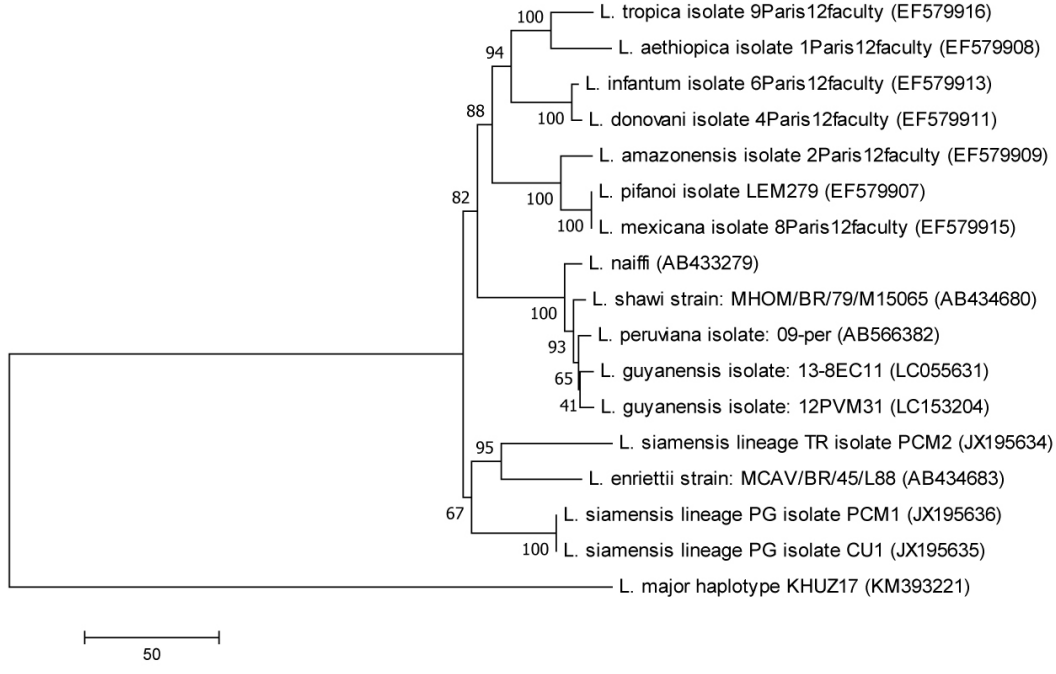
TABLE 1. Baseline characteristics and clinical manifestations of autochthonous leishmaniasis cases reported in Thailand and Myanmar from 1996 to present. *Previously reported as L. siamensis or suspected new species, ¶Level post-treatment.

Case no.	Year	Location	Age (yr)	Sex	Occupation	HIV status (CD4 cells/mm^3)	Other underlying conditions	Clinical classification	Confirmed species	Laboratory investigation				References
										Microscopy (presence of amastigotes)	PCR positive in	Culture	DAT or IFA	
13	2010	Trang	32	F	Teacher	Pos (107)	-	VL, DCL	*L. siamensis*	BM, skin biopsy	Buffy coat, culture	BM +	N/A	5, 23
14	2011	Trang	30	M	Pet store owner	Pos (111)	-	VL, DCL	*L. martiniquensis**	BM, skin biopsy, blood smear	BM, blood, buffy coat, saliva, urine, skin biopsy	BM +	N/A	7, 13, 15
15	2012	Lamphun	52	M	Farmer	Neg	-	VL	*L. martiniquensis**	BM	BM	BM +	N/A	6, 14
16	2012	Chaing Mai	48	M	Industrial worker	Pos (121)	-	VL, DCL	*L. martiniquensis*	BM, skin nodule	BM, skin biopsy	Skin biopsy +, BM +	N/A	6
17	2012	Lamphun	38	M	Lumberjack	Pos (543)	-	VL, DCL	*L. martiniquensis*	BM, skin biopsy	BM, skin biopsy	Skin biopsy +, BM +	N/A	6
18	2012	Lopburi	3	F	Student	Neg	-	CL	N/A	Skin biopsy	N/A	N/A	N/A	8
19	2013	Songkla	28	F	N/A	Pos (617)	-	asymp-tomatic	*L. martiniquensis*	N/A	Saliva	N/A	N/A	15
20	2013	Nakhon Si Thammarat	45	F	Cook	N/A	-	CL	N/A	Skin biopsy	N/A	N/A	N/A	24
21	2015	Kanchanaburi	42	F	Housewife	Pos (89)	TB, PCP	DCL	*L. siamensis*	Skin biopsy	Skin biopsy	N/A	N/A	18
22	2011	Yangon, Myanmar	34	M	N/A	Pos	-	DCL	*L. martiniquensis**	Skin biopsy	Skin biopsy, blood, buffy coat, saliva	N/A	N/A	13
23	2011	Yangon, Myanmar	22	F	N/A	Neg	-	Asymp-tomatic	*L. martiniquensis**	N/A	Buffy coat, saliva	N/A	N/A	13
24	2013	Yangon, Myanmar	60	M	N/A	Neg	Prednisolone used for 2 months, DM	DCL	*L. martiniquensis**	Skin biopsy	Skin biopsy, blood, buffy coat, saliva, urine	N/A	N/A	10, 13

Abbreviations: HIV, human immunodeficiency virus; PCR, polymerase chain reaction; DAT, direct agglutination test; IFA, indirect immunofluorescence assay; N/A, not available; AIHA, autoimmune hemolytic anemia; DM type 2, diabetes mellitus type 2; HT, hypertension; TB, tuberculosis; HCV, hepatitis C virus; IVDU, intravenous drug use; PCP, pneumocystis carinii pneumonia; VL, visceral leishmaniasis; DCL, diffuse cutaneous leishmaniasis; CL, cutaneous leishmaniasis; BM, bone marrow; LN, lymph node



1A



1B

Fig 1. Unrooted phylogenetic trees were derived from 2 genetic loci [ITS1 (A) and CYT B (B)] using the Neighbor Joining Method.[66] The percentage of replicate trees in which the associated taxa clustered together during the bootstrap test (1,000 replicates) is shown next to the braches.[67] The trees are drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic trees. The evolutionary distances were computed using the number of differences method[68], and are in the units of the number of differences per sequence. Codon positions included were 1^{st} + 2^{nd} + 3^{rd} + noncoding. All positions containing gaps and/or missing data were eliminated. Evolutionary analyses were conducted using Molecular Evolutionary Genetics Analysis (MEGA) software version 7.[69]

TABLE 2. Genbank accession numbers of suspected novel Leishmania species from autochthonous leishmaniasis cases reported from Thailand and Myanmar. The names of both suspected and confirmed species are shown.

Case no.	Year	Location	Age (yr)	SSU-rRNA	ITS1	HSP70	CYT B	RPOIILS	Suspected species	Confirmed species	References
3	2005	Phang Nga	55	JN885899	EF200012	N/A	JX195636	N/A	Suspected a novel species (*L. siamensis* lineage PG, isolate PCM1)	*L. martiniquensis**	17, 20, 21, 26
8	2008	Chiang Rai	45	N/A	N/A	N/A	N/A	N/A	Suspected *L. siamensis*	*L. martiniquensis**	13
9	2008	Chantaburi	37	N/A	GQ226034	N/A	N/A	N/A	Suspected a novel species (*L. siamensis*, isolate CU)	*L. martiniquensis**	16, 21
11	2009	Songkla	46	JX195633	JX195639 JQ001751 KU050860-KU050862 (saliva, buffy coat, and tissue)	KC202883	JX195635	N/A	Suspected a novel species (*L. siamensis*, lineage PG, isolate CU1/LEBM-So)	*L. martiniquensis**	7, 12, 13, 15, 20, 26
12	2010	Satun	5	JN087497	JX195637	KC202882	N/A	N/A	Suspected *L. siamensis* (*L. siamensis* lineage PG, isolate PCM4)	*L. martiniquensis**	11, 20
13	2010	Trang	32	JQ280883	JX195640	KC202880	JX195634	JQ586202	Suspected *L. siamensis* (*L. siamensis* lineage TR, isolate PCM2)	*L. siamensis*	5, 23
14	2011	Trang	30	N/A	JQ001752 KU050856-KU050859 (blood, buffy coat, and tissue) KF227887-KF227892 (bone marrow, blood, saliva, urine, and tissue biopsy)	N/A	N/A	N/A	Suspected a novel species (*L. siamensis*, lineage PG, isolate LEBM-Pi/PCM5)	*L. martiniquensis**	7, 13, 15, 26

*Sequence: 100% identical to the sequence previously reported (not submitted as a new accession number)

Abbreviations: SSU-rRNA, small subunit ribosomal ribonucleic acid; ITS1, internal transcribed spacer 1; HSP70, heat shock protein 70; CYT B, cytochrome B; RPOIILS, RNA polymerase II largest subunit; N/A, not available

TABLE 2. Genbank accession numbers of suspected novel Leishmania species from autochthonous leishmaniasis cases reported from Thailand and Myanmar. The names of both suspected and confirmed species are shown.

Case no.	Year	Location	Age (yr)	SSU-rRNA	ITS1	HSP70	CYT B	RPOIILS	Suspected species	Confirmed species	References
15	2012	Lamphun	52	N/A	JX898938	KP244366	N/A	KM677933	*L. martiniquensis*	*L. martiniquensis* (LSCM1)	6, 14
16	2012	Chiang Mai	48	N/A	KJ210834 KJ210835	KP244367	N/A	KM820665	*L. martiniquensis*	*L. martiniquensis* (LSCM2)	6
17	2012	Lamphun	38	N/A	KJ210836 KJ210837	KP244368	N/A	KM820666	*L. martiniquensis*	*L. martiniquensis* (LSCM3)	6
19	2013	Songkla	28	N/A	KU050863 (saliva)	N/A	N/A	N/A	*L. martiniquensis*	*L. martiniquensis*	15
21	2015	Kanchanaburi	42	N/A	KX347438	N/A	N/A	KX347439	*L. siamensis*	*L. siamensis*	18
22	2011	Yangon, Myanmar	34	N/A	N/A	N/A	N/A	N/A	Suspected *L. siamensis*	*L. martiniquensis**	13
23	2011	Yangon, Myanmar	22	*Identical to GQ226033 (saliva and buffy coat)	N/A	N/A	N/A	N/A	Suspected *L. siamensis* (*L. siamensis*, isolate CU)	*L. martiniquensis**	13
24	2013	Yangon, Myanmar	60	N/A	*Identical to JQ001751	N/A	N/A	N/A	Suspected *L. siamensis* (*L. siamensis*, isolate LEBM-So)	*L. martiniquensis**	10, 13

*Sequence: 100% identical to the sequence previously reported (not submitted as a new accession number)

Abbreviations: SSU-rRNA, small subunit ribosomal ribonucleic acid; ITS1, internal transcribed spacer 1; HSP70, heat shock protein 70; CYT B, cytochrome B; RPOIILS, RNA polymerase II largest subunit; N/A, not available

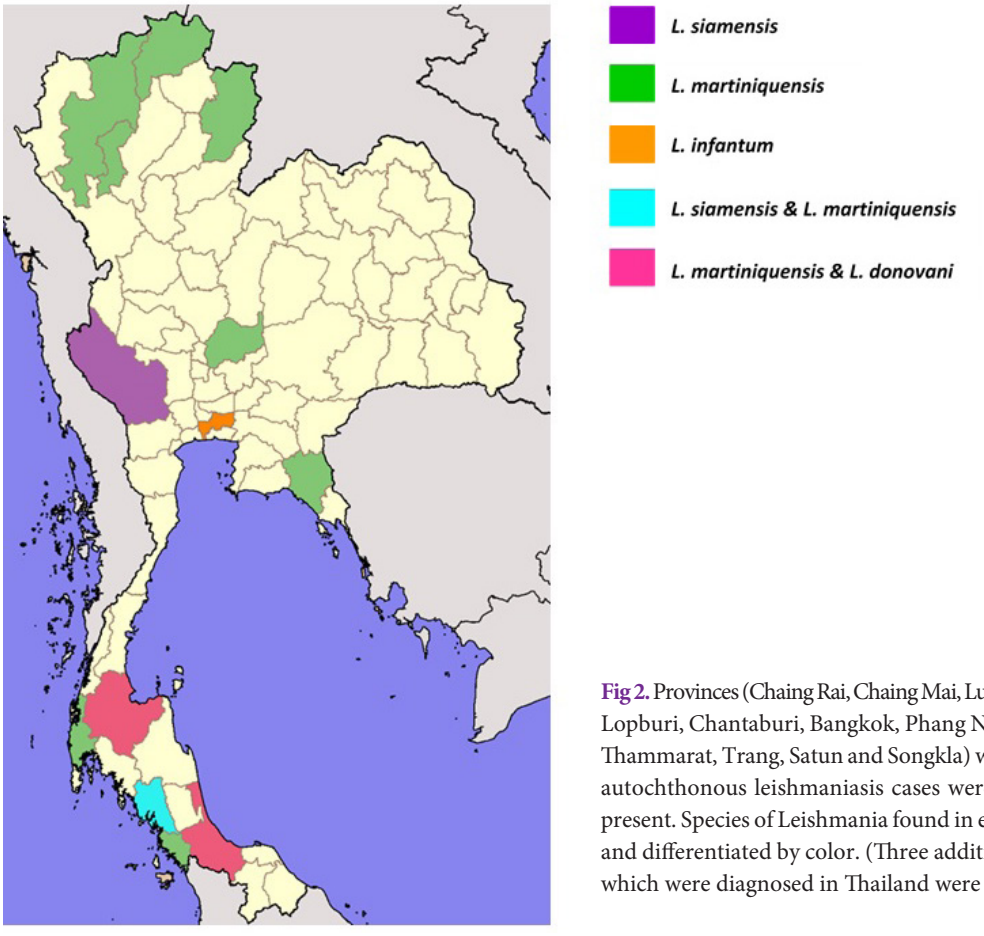


Fig 2. Provinces (Chaing Rai, Chaing Mai, Lumphun, Nan, Kanchanaburi, Lopburi, Chantaburi, Bangkok, Phang Nga, Surat Thani, Nakorn Si Thammarat, Trang, Satun and Songkla) within Thailand from which autochthonous leishmaniasis cases were reported during 1996 to present. Species of Leishmania found in each province are described and differentiated by color. (Three additional cases from Myanmar which were diagnosed in Thailand were not included in the map.)

L. martiniquensis is a major cause of autochthonous leishmaniasis in Thailand. *L. martiniquensis* is a rare Leishmania species that was originally discovered on Martinique Island.[28,29] Human cases of *L. martiniquensis* infection have only been sporadically reported from locations that include Martinique Island, Thailand and Myanmar.[26,28,29] In addition to being reported as a cause of human leishmaniasis, *L. martiniquensis* was found to cause CL in horses in Germany and Switzerland,[42] in bovines in Switzerland[43] and a horse in the United States.[44] Moreover, *L. martiniquensis* is closely related to *L. enrietti* complex which mainly infects domestic guinea pigs, suggesting its zoonotic nature.[1,26,27]

L. siamensis is a novel *Leishmania* species that was first discovered in Thailand.[17,18] Only two cases of confirmed *L. siamensis* cases have been reported in the world and both were reported in Thailand.[17,18] Both cases had HIV co-infection with absolute CD4 count < 200 cells/mm^3 (Table 1). The first case developed VL[17] and the second case had DCL.[18] In their January 2017 review, *Leelayoova* et al., mentioned their preliminary unpublished finding that asymptomatic *L. siamensis* infection was observed in both immunocompetent and immunocompromised individuals.[27] No animal infection by *L. martiniquensis* has been reported. Overall, little is known about this novel *Leishmania* species.

L. donovani and *L. infantum* are species that commonly cause VL in India, Bangladesh, Nepal and Sudan. A few autochthonous cases caused by these 2 species have also been reported from Thailand (Table 1).[9,20,21,25] These two species are closely related members of the genus *Leishmania*. Given that both species are established, detailed information relating to their biology, taxonomy classification, epidemiology, and clinical manifestations are not mentioned in this review.

Diagnosis of leishmaniasis relies on clinical presentation and laboratory findings. Laboratory diagnosis of leishmaniasis is based on identification of *Leishmania* amastigotes in smear or tissues, by *in vitro* parasite cultivation, by molecular detection of parasite DNA and/or by serology testing of parasite antibody.[2,45,46] Definite diagnosis is confirmed when direct evidence of the presence of parasites, parasite DNA or positive culture is detected.[45,46] Serology testing such as direct agglutination test (DAT), recombinant K39 antigen based immunochromatographic test, immunofluorescence antibody assay (IFA) and enzyme-linked immunosorbent assays (ELISAs) can be used to support a diagnosis,

but the sensitivity of the test depends on host immune status.[46-48] In immunocompromised patients such as patients with HIV, test sensitivity is diminished and false-negative results are often observed.[47,48] However, parasitic loads in immunocompromised patients are usually high which increases the sensitivity of culture and molecular detection.[47,48] Accordingly, appropriate laboratory investigations should be employed and results should be interpreted taking all of the aforementioned factors into consideration before definite diagnosis is established.

Clinical manifestion of *L.martiniquensis* and *L.siamensis* infection

Various clinical presentations including asymptomatic, CL and VL, have been observed in individuals infected with *L. martiniquensis* or *L. siamensis* and these presentations are clinically similar to those observed in *L. donovani* and *L. infantum* infection. In disease endemic areas, the majority of *Leishmania* infected individuals are asymptomatic, especially in people with intact cell-mediated immunity.[48] Immunity defects such as children aged < 5 years, poor nutritional status, HIV co-infection and prolonged immunosuppressive drug use increases the susceptibility of an individual to develop symptomatic leishmaniasis.[48,49]

Of 13 reported cases of *L. martiniquensis* (10 Thai and 3 Burmese), two were symptomatic and 11 developed various clinical symptoms including CL and VL. Nine of 11 of symptomatic cases had VL. The main clinical symptoms found in VL cases included hepatomegaly (66.7%), splenomegaly (66.7%), prolonged fever (55.6%), and weight loss (33.3%). Bleeding tendency was also observed which was associated with thrombocytopenia. Abnormal laboratory findings in the VL group included anemia (100%), thrombocytopenia (88.9%), leukopenia (55.6%), pancytopenia (44.4%), elevated SGOT/SGPT or abnormal alkaline phosphatase (44.4%), hypoalbuminemia (44.4%) and hypergammaglobulinemia (44.4%). Interestingly, 8 of 13 *L. martiniquensis* cases were co-infected with HIV. Most HIV infected individuals had absolute CD4 < 200 cells/mm^3. Of the 8 HIV infected patients, 6 (75%) cases developed VL. Remarkably, 5 of the 6 HIV infected patients who developed VL had at least one cutaneous lesion. In contrast, all non-HIV infected patients presented with or developed VL without skin lesions or disseminated CL without visceral organ involvement. These findings suggest that clinical presentations of *L. martiniquensis* infection are influenced by host immunity.

Cutaneous manifestations in reported *L. martiniquensis* and *L. siamensis* infection have ranged from single localized to diffuse cutaneous lesions. Skin manifestations vary from erythematous papules, nodules, plaques and ulcers. All lesions were chronic, discrete and painless, resembling lepromatous leprosy, but no neurological invasion was involved. Lesion distribution ranged from primary lesion at the exposed area to widely disseminated lesions throughout the body. Most reported CL cases had multiple diffuse cutaneous lesions, similar to what is typically observed in cases of New World leishmaniasis. However, a few Old World *Leishmania* species, (e.g., *L. aethiopica*) can also cause DCL. This condition is associated with impaired cell-medicated immunity which facilitates the dissemination of the parasite in subcutaneous tissues. Association between host immunity and cutaneous presentations was also observed in the reported cases because DCL was primarily found in HIV infected individuals. Skin lesions found in *L. martiniquensis* and *L. siamensis* reported cases are described in Table 3.

Potential vectors and reserviors

The only confirmed vector of leishmaniasis is a female Phlebotomine sandfly. There are more than 800 known sandfly species, with 464 and 372 species discovered in the New World and Old World, respectively.[1] Not all sandfly species are thought to be capable of transmitting the disease, as only about 30 sandfly species are proven vectors of human leishmaniasis.[50,51] Old World sandflies include three genera (*Phlebotomus, Sergentomyia* and *Chinius*) and New World sandflies include three genera (*Lutzomyia, Warileya* and *Brumptomyia*).[1] Genus *Phlebotomus* and *Sergentomyia* are the major vectors of Old World while genus *Lutzomyia* is the primary New World vector.[1,50] Sandflies are mostly nocturnal, because they are not able to withstand dehydration.[50] In the New World, they are often found in caves and tree buttress roots while New World sandflies inhabit the contaminated soils of farm animal shelters, termite nests, rodent burrows and land under houses inhabited by humans.[50] They are short distance flyers, flying an average of 1.5 km per day.[1,50] Surveillance studies of sandfly species in Thailand were performed at various time points which showed that all 3 genera of Old World sandflies (*Phlebotomus, Sergentomyia* and *Chinius*; and some articles added *Idiophlebotomus* to the list as an additional genus, but currently *Idiophlebotomus* is a subgenus of genus *Phlebotomus*), with approximately 27 species being identified in the southern, central, northern and western regions of Thailand.[52-65] *S. gemmea* was the most common species found in the northern and southern regions[58,59,65], whereas *S. hodgsoni, S. anodontis* and *N. vietnamensis* were prominent species found in

TABLE 3. Clinical manifestations of skin lesions observed in patients infected with either *L. martiniquensis* or *L. siamensis*

Case no.	HIV status	Clinical classification	Characteristics of cutaneous lesions	Lesion distribution	References
8	Pos	VL, DCL	Lumpy skin lesions	ND	13
11	Pos	VL, CL	Single painless well-defined punched-out ulcer surrounded by erythematous plaque with serous oozing and granulation tissue on top (3 x 3 cm in size)	Left knee	7, 12, 13, 15
14	Pos	VL, DCL	Generalized painless discrete well-defined dusky red infiltrative papules and plaques with ulcers Punched-out ulcer surrounded by erythematous plaque with purulent discharge and granulation tissue on top (2 x 2 cm in size)	Torso, face, and extremities Right leg	7, 13, 15
16	Pos	VL, DCL	Hyperpigmented nodules Multiple discrete firm hypopigmented and brownish papules and nodules	Face, both elbows, and later extended to both hips and legs Inner canthi, eyelids, nose, helices/antihelices of pinnae, and extensor surfaces of hands, forearms (prominence over knuckles, elbows, ulnar ridges, knees, tibial crests, malleoli, buttocks, palm, and soles)	6
17	Pos	VL, DCL	Multiple discrete hypopigmented papules and nodules Multiple hypopigmented sclerotic plaques	Inner and outer canthi of eyes, helices/antihelices of both pinnae and extensor surfaces of hands, forearms, and legs (prominence on knuckles, elbows, ulnar ridges, knees, tibial crests, and malleoli) Palms	6
21	Pos	DCL	Multiple painless well-defined non-ulcerated erythematous to indurated hyperpigmented plaques and nodules varying in size; some atrophic hyperpigmented plaques; and, a few scattered erythematous macules and patches	Face and both legs Face Torso	18
22	Pos	DCL	Multiple umbilicated erythematous papules	Neck, arms, and chest wall	13
24	Neg	DCL	Multiple erythematous skinny infiltrative erythematous plaques and nodules with some developed ulcers	Face, torso, and all extremities	10, 13

Cases 8, 11, 14, 16, 17, 22, and 24 were infected with *L. martiniquensis* and case 21 was infected with *L. siamensis*.

Abbreviations: HIV, human immunodeficiency virus; ND, not described; VL, visceral leishmaniasis; DCL, diffuse cutaneous leishmaniasis

some certain specific areas.[52,55,64] Although many sandfly species have been detected in Thailand, not all species have been proven to be vectors for leishmaniasis. Only one study reported the presence of *Leishmania* DNA in captured sandflies.[58] *Leishmania* ITS1 and HSP70 genes, similar to nucleotide sequences of *L. martiniquensis*, were detected in *S. gemmea* and *S. barraudi*, which suggest their role as potential vectors.[58]

A few studies were conducted to identify animal reservoirs in disease endemic areas of Thailand.[17,20,21,25] Some direct (presence of *Leishmania* in reservoirs) and indirect (serology) evidence exists that strongly suggests that domestic animals may serve as natural reservoirs of the disease.[17,20,21,25] A few reported studies set forth to detect *Leishmania* antibody by direct agglutination test (DAT). Those studies found DAT test to be reactive in some domestic animals, such as dogs, cats, rats and cattle that were living or kept near the residence or housing of infected individuals.[17,20,21,25] However, only one study found direct evidence that suggested the presence of *Leishmania*.[7] *L. martiniquensis* DNA was detected by PCR of ITS1 and HSP70 genes in black rats (*Rattus rattus*) that were captured near the residence of infected patient's.[7] In addition, CL caused by *L. martiniquensis* was observed in Europe and America in farm animals.[42-44] Thus, the data suggests that *L. martiniquensis* transmission is likely zoonotic.

CONCLUSION

Leishmaniasis is a disease that was once considered rare in Thailand, given that all identified cases were thought to be imported. However, a number of autochthonous leishmaniasis cases have been reported since 1996 in patients who had no history of traveling abroad. The majority of these cases suffered from *L. martiniquensis* infection. However, a novel species of *Leishmania*, namely *L. siamensis*, which was first and only discovered in Thailand was found to be the causative pathogen in two confirmed cases of leishmaniasis. Black rats may serve as a natural reservoirs, suggesting it is zoonotic in nature. Two sandfly species, *S. gemmea* and *S. barraudi*, may be able to transmit the disease. The update knowledge on emerging leishmaniasis situation in Thailand emphasizes potential problematic public health concern especially in HIV-infected patients. Future research focusing on epidemiology of the disease, potential vectors and reservoirs are indeed required for public health prevention and control. Early diagnosis of leishmaniasis in HIV-infected individuals should be performed in patients who have clinical manifestations suspicious of leishmaniasis. Moreover, in-depth studies on biology of novel *Leishmania* species and host parasite immunity are crucial for drug development since there are limited effective medical treatment options available for this disease.

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2018

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

anesthesiology siriraj

6th International Pain Forum and Cadaveric Workshop, the 30th Anniversary Siriraj Pain Management Clinical Training Center

21–23 January 2019

Two-day lectures and one-day workshops

Lecture venue: 21–22 January 2019 Siriraj Medical Research Center (SIMR) ,
Workshop venue: 23 January 2019 Siriraj Training and Education Center for Clinical Skills (SiTEC) 4th floor Sri Savarinthira building, Siriraj hospital

MONDAY 21 JANUARY 2019: NON-CANCER PAIN

- The classic and the new versions of the common problems in chronic pain management (Thai)
- Seven articles pain specialists must know and reasons why
- Controversy in pain management
- What's new in spinal cord stimulation?
- Prolotherapy and regenerative medicine, the fountain of youth?
- Head-to-toe common sonographic scanning for pain medicine: live demonstration

TUESDAY 22 JANUARY 2019: CANCER PAIN

- Pain and opioids situation in Thailand
- Cancer pain in children, the neglected child
- Cancer pain practice at MD Anderson and opioids crisis in the US
- New opioids in cancer pain management
- Common interventions for cancer pain
- Intrathecal therapy for cancer pain and non-cancer conditions

WEDNESDAY 23 JANUARY 2019: MASTERCLASS AND WORKSHOPS

08:00–11:30 **Morning session**



Spinal cord stimulation masterclass

An intensive cadaveric masterclass. Step by step hands-on training starts from epidural access, tunneling and pocketingwith dedicated fluoroscopy, cadaver and speakers for each group.



Ultrasound guided pain intervention workshop

Live demonstration and ultrasound scanning focus on chronic non-cancerpain intervention. Four stations of hands-on experiences as follows;

1) Cervical MBB, GON, stellate ganglion block
2) Intra-articular injection (shoulder, hip, knee)
3) Spine sonography (thoracic, lumbar, TPVB, intercostal)
4) Caudal, Sacroiliac joint, piriformis, pudendal injection



12:30–16:00 **Afternoon session**

Interventional cancer pain cadaveric workshop



Fluoroscopic-guided cadaveric workshop with MD Anderson team. Four stations of hands-on experience as follows;

1) Intrathecal pump (interrogation, access and refill)
2) Intrathecal access (IDDS and port)
3) Celiac and splanchnic neurolysis
4) Superior hypogastric and ganglion impar neurolysis



Regenerative medicine live demonstration

Live demonstration on scanning, preparing and injecting with the regenerative medicine expert.

SPEAKERS

Billy Huh, Thomas Chai, Carlos Roldan; MD Anderson Cancer Center, Houston, Texas, USA.
Phillippe Mavrocordatos; Cecil Pain Management Center, Lausanne, Switzerland
Peter Courtney; Royal Melbourne Hospital, Melbourne, Australia
Gerald Chai; Chatham Orthopaedic Associates, Savannah, Georgia, USA
Carina Li; Hong Kong Pain Medicine Centre, Hong Kong
Donald Tang; Veterans General Hospital, Chia-Yi, Taiwan
Oraphan Thongtang, Pongparadee Chaudakshetrin, Pradit Prateepavanich, Wanna Srirojanakul, Nantthasorn Zinboonyahgoon, Pranee Rushatamukayanunt, Pramote Euasobhon, Sahatsa Mandee, Taniga Kiatchai, Bunpot Sitthinamsuwan, Sasikaan Nimmaanrat, Nuj Tontisirin, Marvin Thepsoparn, Patt Pannangpetch; Thailand



REGISTRATION FEE

- Two-day lecture: 3,500 Baht (110 USD),
  Early bird (within 31/12/18) 3,000 Baht (95 USD);
- Spinal cord stimulation masterclass: 8,500 Baht (270 USD); 12 participants OR
  Ultrasound guided pain intervention workshop: 3,500 Baht (110 USD); 20 participants
- Interventional cancer pain cadaveric workshop: 5,500 (180 USD); 20 participants OR
  Regenerative medicine: 3,500 Baht (110 USD); 10 participants

CONTACT

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