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Introduction

The Journal of Southeast Asian Medical Research is a peer-reviewed journal with printing every 6 months. The main goal of this collaboration project is to distribute new knowledge in medical sciences to medical communities and scientists, as well as encouraging scientific collaborations within Southeast Asia and also other nations around the world. The journal publishes original research in the medical sciences: clinical and basic. We welcome original articles from across the world. The editorial board consists of international experts in various fields of medicine, ranging from internal medicine to a variety of surgeries. The full text of the journal is available online at http://www.jseamed.org

It is our aim to publish the most up-to-date and useful research information in medical sciences. In Southeast Asia, there are some unique problems in health care and diseases, such as tropical diseases, and it is crucial that health professionals can access, share and exchange knowledge promptly. In this region, there is still a gap of knowledge in health sciences that needs to be closed by scientific research, which we are hoping to close after this collaboration project. We hope that the journal will fulfill the objectives and will provide benefit to all, both medical practitioners and researchers alike.

Editorial board

JOURNAL OF SOUTHEAST ASIAN MEDICAL RESEARCH

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PREVALENCE, ASSOCIATED FACTORS AND REINTERVENTION RATE OF ENDOLEAKS AFTER THORACIC ENDOVASCULAR AORTIC REPAIR AMONG PATIENTS WITH THORACIC AORTIC ANEURYSMS, PHRAMONGKUTKLAO HOSPITAL, BANGKOK, THAILAND

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Abstract

Background: Endoleaks are one of the complications seen after endovascular repair of thoracic aortic aneurysms (TAA). The study evaluated the prevalence, associated factors and reintervention rate, the classified type of endoleaks and the outcomes of secondary interventions among patients with endoleaks.

Methods: Between 2010 and 2020, medical and radiologic data of all patients receiving a diagnosis of TAA treated by thoracic endovascular aortic repair (TEVAR) and undergoing postoperative CT angiogram at Phramongkutklao Hospital were retrospectively reviewed and analyzed.

Results: Over a median follow-up of 569 days (IQR=93-1256), 6 of 26 (23.08%) patients developed endoleaks, of which 50% (3 of 6) were type I, 16% (1 of 6) were type II, IV and V each and none were type III. The median aneurysm diameter was 62 mm (IQR=52.5-75.5). Endoleaks were associated with younger age (p<0.05) and a higher percentage of graft oversizing over the aorta distal to the aneurysm (p=0.014). All patients with endoleaks underwent reintervention (100%) with good outcomes.

Conclusion: Endoleaks were detected in one of the four patients treated with TEVAR during follow-up, particularly when they were young or exhibited a too oversized graft over the aorta distal to the aneurysm. All patients with endoleaks underwent reintervention with good outcomes.

Keywords: Endoleaks, Thoracic aortic aneurysm, Thoracic endovascular aortic repair, Stent-graft
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Introduction

Conventional open repair of a thoracic aortic aneurysm (TAA) remains a major invasive surgical procedure with significant inherent risk. These operations require a thoracotomy, aortic clamping, partial aortic bypass to support circulation and considerable blood loss with associated transfusions.[1] The surgical mortality rate may approach 12% even when performed by experienced surgeons among patients with a good cardiac reserve and deemed excellent surgical candidates.[2] Perioperative morbidities

in this referenced cohort included spinal cord ischemia among 14%, respiratory failure among 20% and renal insufficiency among 13% of patients undergoing open repair.[2]

Endovascular techniques are now used to treat thoracic aortic aneurysms (TAAs). This endovascular approach (TEVAR) offers a subset of patients with TAA a less invasive procedure to exclude their aneurysms.[3] It has also altered how patients follow up after TAA repair.[2]

Endoleaks have been pointed out as adverse events causing migration of the stent-graft and rupture of the aneurysm; and therefore, need to be detected during follow-up.[4]

Although detecting and managing endoleaks after EVAR have been well described, less is known about endoleaks after TEVAR.[3] This investigation evaluated the prevalence and determinants of endoleaks and the outcomes of secondary interventions among patients with endoleaks after endovascular repair of TAAs.

Methods

Study design and subjects

This study was approved by the Institutional Review Board Royal Thai Army Medical Department (No. IRBRTA 1431/2563). Permission to Access Medical Records and ICD-10 was approved. Regarding using secondary data, a waiver of informed consent was granted.

Phramongkutklao Hospital is a 1200-bed tertiary hospital in Bangkok, Thailand, where TEVAR cases have been performed since 2010. Nonetheless, studies about endoleaks have not been conducted at this center. Between 2010 and 2020, medical and radiologic data of all patients receiving a diagnosis of thoracic aortic aneurysms treated by TEVAR and undergoing postoperative CT angiogram were retrospectively reviewed, as shown in **Table 4**. Patients not following up CTA study were excluded. All TEVAR were performed in the context of Food and Drug Administration trials with the Medtronic Valiant (Medtronic AVE; Santa Rosa, CA, USA), the Cook TX2 & Cook alpha (Cook Medical; Bloomington, IN, USA), the E-vita OPEN PLUS (JOTEC GmbH; Lotzenäcker, Hechingen, Germany) and the Terumo aortic (Bolton Medical; Sunrise, FL, USA) devices. After aneurysmal repair, imaging using triple-phase computed tomographic angiography (CTA) was performed at 1, 6 and 12 months after stent-graft implantation and annually after that. More frequent examinations were performed when clinically indicated. CTA was performed using a multidetector scanners (64-slice or 160-slice CT). The three-phase CTA consisted of a noncontrasted scan through the chest and upper abdomen, followed by a chest and abdominal CTA using 120 mL of nonionic contrast. A 2-minute delayed computed tomographic scan was performed through the chest and upper abdomen. [4]

Data collection

Preoperative clinical data of each patient, i.e., demographics, comorbidities, preoperative condition and radiologic data, such as TAA morphologic measurements, were reviewed by a diagnostic radiology resident under the supervision of an interventional radiologist. The radiologic data were reviewed at two different times and compared with the official report's data. The high intra- and interobserver agreement levels were exhibited in the data regarding diameter, length, morphology, nature and site of the aneurysm. A level of almost perfect was obtained for intra- and interobserver agreement of morphology and nature of the aneurysm as well as the interobserver agreement of the site of the aneurysm.[5] Additionally, a substantial level was exhibited in the intraobserver agreement of the site of the aneurysm.[5] The data are shown in the supplementary table.

Intraoperative data collected consisted of the size, number and type of stent-graft used, the left subclavian artery (LSA) coverage, section of aorta coverage by stent-graft, proximal & distal landing zone, oversizing and the presence of immediate endoleak on completion of the arteriogram.

Postoperative clinical events, such as secondary endovascular or surgical interventions, major complications and mortality were reported. In addition, radiologic data, including TAA diameter, aneurysmal sac expansion, and types

of the endoleak were also recorded during follow-up. The diagnosis of the endoleak and its type was performed on CTA examinations evaluated on the picture archiving and communication system (PACS) workstations with multiplanar reformatting capabilities to classify the endoleak type. Endoleaks were classified as type I based on their location in contiguity with the proximal or distal sealing zone, as well as early filling of the TAA sac. Endoleaks were classified as type II if they could not be seen communicating with either the distal or the proximal sealing zones or, in the case of delayed enhancement of the sac. Type III endoleak was classified based on association with a disjunction of two stent grafts.[6] Changes in TAA diameters were evaluated using standardized maximal aortic sac diameter measurements. The mean changes in maximal aortic diameter were calculated by comparing the baseline aortic diameter with the maximal diameter at the last follow-up in the sagittal plane on CTA, irrespective of endoleak treatment.

Definition

Oversizing was defined as the percent difference between the stent graft diameter and the diameter of the aorta deployed.[7] Results of patients undergoing reintervention were described as good outcomes or successful in the case of the endoleak being totally resolved in the intraoperative angiography without any acute intraoperative complications.

Statistical analysis

Data were analyzed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Continuous data between non-parametric distribution continuous data were assessed using the Mann-Whitney U test or independent t-test. In addition, Fisher's exact test was used to analyze categorical data. All statistical analyses were two-tailed, and a significance level of 0.05 was used to calculate the proportion.

Results

Baseline characteristics and preoperative conditions

The study included 26 patients treated consecutively for a TAA by TEVAR during the observation period; 16 were male and 10 were female. Ages ranged from 27 to 87 years, with a mean of 68.73 ± 12.85 and a median of 71 (IQR = 63.5 to 78.5). No patients were excluded due to poor image qualities. The median follow-up period was 569 days; IQR = 93- 1256. The following data are shown in **Table 1**. A total of 95 CTA studies were reviewed. Six endoleaks were detected in 6 of 26 (23.08%), as described in **Table 2.** Among these aneurysms, 22 were degenerative ones; two were dissecting aneurysms, one was postdissecting aneurysm, and one was a pseudoaneurysm developed on the penetrating ulcer of the thoracic aorta. At the time of TEVAR, the median TAA diameter was 62 mm (IQR = 52.5-75.5), and the median TAA length was 67.5 mm (IQR = 43.5-85), as described in Table 3. A total of 34 stent-grafts (16 Cook TX2, 3 Cook alpha, 4 Medtronic Valiant, 2 E-vita OPEN PLUS and 1 Terumo aortic) were used for TAA exclusion (1.31 per patient) for a median length of aortic coverage of 166 (IQR = 150-216) as described in **Table 4**. In the endoleak group, 50% (3 of 6) exhibited endoleak type I as shown in **Figure 1**, 16.67% (1 of 6) type II, as shown in **Figure 2**, none of type III, 16.67% (1 of 6) type IV as shown in **Figure 3** and 16.67% (1 of 6) type V (**Figure 4**). Three endoleaks (50%) were diagnosed on the first postoperative CTA within the first month, and the rest (50%) were detected during follow-up. Patients with endoleaks and their management after diagnosis are described in **Table 5.**

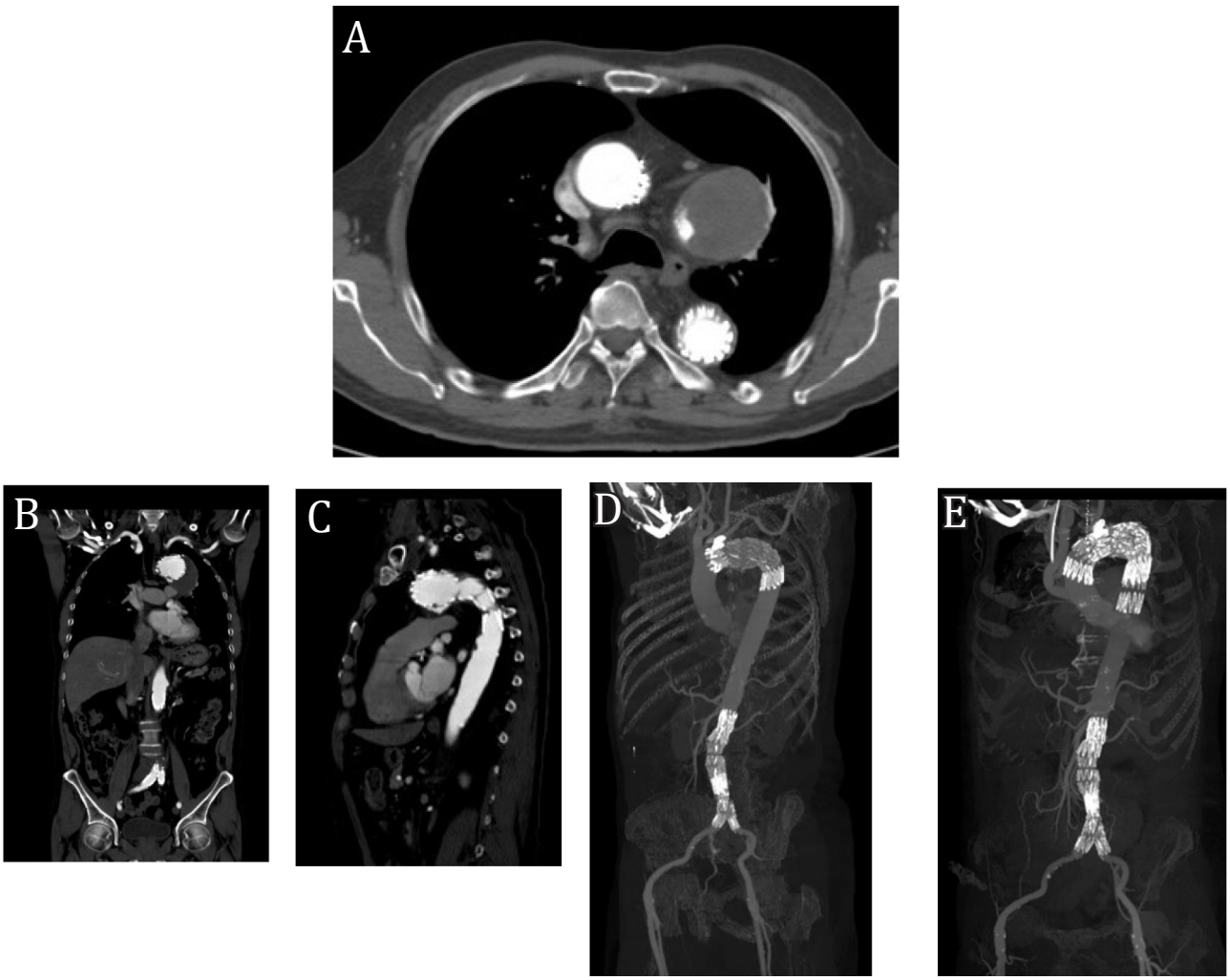

Figure 1. Radiographic feature of endoleak type IA, A., B., C. CTA shows contrast leakage at the proximal aortic stent. D. CTA with 3D reconstruction shows an endovascular aortic stent- graft at the aortic arch, just at the level of the origin of the left common carotid artery cover to the mid-descending thoracic aorta. E. CTA with the 3D reconstruction of the same patient, posttreatment for 6 months, demonstrated a new stent-graft at the aortic arch, inner to the previous stent, and covering more on the descending thoracic aorta. Note the stent-graft at the abdominal aorta.

Table 1. Demographic data and comorbid conditions of patients

	N (n=26)	**%**
Age		
Mean ± SD	68.73 ± 12.85	
Median (IQR)	71 (63.5 – 78.5)	
Sex		
Male	16	61.54
Female	10	38.46
Hypertension	18	69.23
Diabetes mellitus	6	23.08
Dyslipidemia	10	38.46

Table 1. Demographic data and comorbid conditions of patients (Cont.)

	N (n=26)	%
Coronary artery disease	5	19.23
Renal insufficiency	5	19.23
Abdominal aortic aneurysm	4	15.38
length of follow up (day)		
Mean ± SD	767.81 ± 736.66	
Median (IQR)	569 (93 - 1256)	

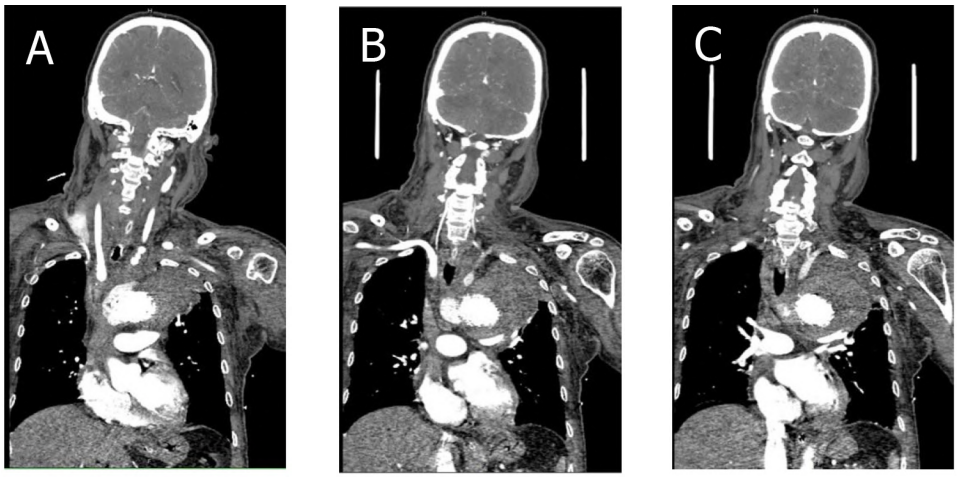

Figure 2. The radiographic appearance of endoleak type II, A., B., C. Computed tomographic angiography demonstrated contrast enhancement in the periphery of the aneurysmal sac. Blood flow retrograded from the residual proximal left subclavian artery and left vertebral artery.

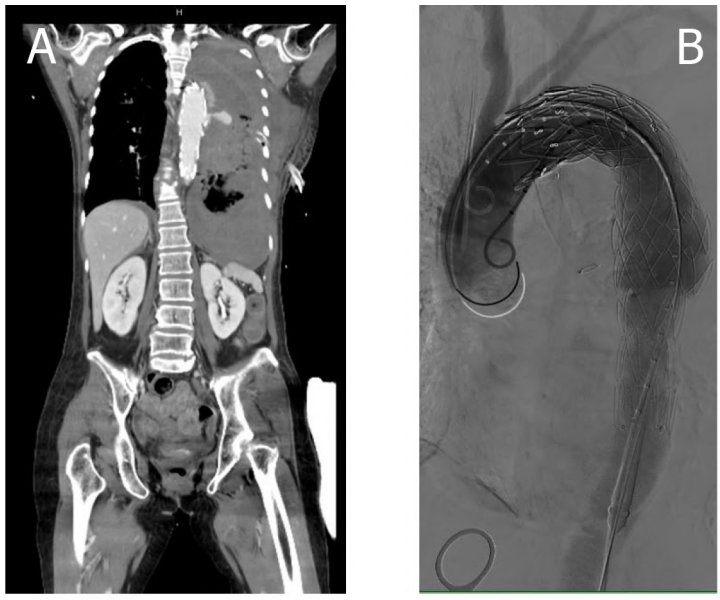

Figure 3. Radiologic appzearance of endoleak type IV, A. computed tomographic angiography shows peri-graft hematoma and contrast leakage at the mid-graft level. B. angiography on the same day shows no graft kink, narrowing, collapse or migration.

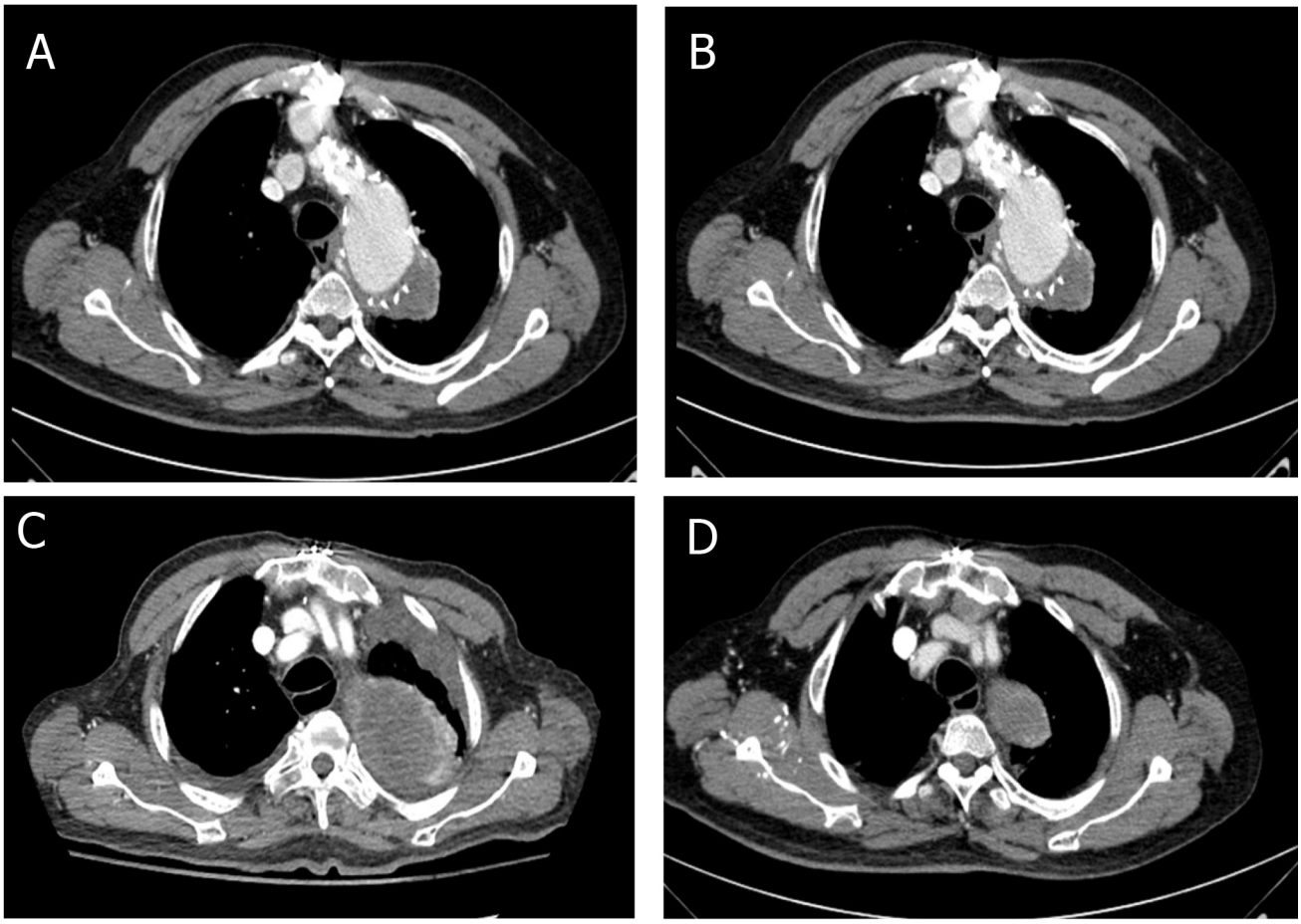

Figure 4. Endoleak type V, A., B. computed tomographic angiography shows a thrombosed fusiform aneurysm at the proximal descending thoracic aorta. C., D. CTA of the whole aorta in the next 4 years of the same patient demonstrated a significant increase in the size of the thrombosed aneurysmal sac at the proximal descending aorta and new left hemothorax.

Patients who developed endoleaks were younger than those who did not (64.17± 5.78 vs. 70.10 ± 14.14 years old; p=0.041) but a wider range of age was noted in the nonendoleak group than in the endoleak group (range 27 to 87 vs. 56 to 74 years old). However, the sex ratio and prevalence of comorbidities showed no statistical difference (**Table 2**). In addition, days of follow-up among patients with endoleaks were more than those without endoleaks (1337 vs. 536 days).

Morphologic characteristics of TAA at the time of interventions are shown in **Table 3**. The extension of TAAs was comparable at the time of intervention, with similar diameter and length among both groups. The nature and morphology of aneurysms did not differ between the two groups. In addition, the location of the aneurysm along the thoracic aorta, including ascending, arch and descending parts, showed similarity in both groups (p=0.999).

Peroperative conditions

Peroperative conditions and technical considerations are shown in **Table 4**. The percentage of graft oversizing over the aorta distal to the aneurysm among patients with endoleaks was higher among those in the nonendoleaks group (49 vs. 29%; p=0.014). The percentage of proximal graft oversizing in the endoleak group was also more than in the non-endoleak group (40 vs. 27%; p=0.055). No differences were observed in the mean diameter of proximal and distal sites, length and the number of stent grafts used for TEVAR in the two groups. The mean length of proximal and distal landing zones and the section of the aorta treated by stent-grafts showed no difference in the two groups (p=0.748, p=0.077

and p=0.737, respectively). Intentional coverage of the LSA to extend the proximal landing zone of the stent-graft (p=0.16) and the urgent character of TEVAR (10 of 26; p=0.644) did not affect the occurrence of endoleaks during follow-up. More patients in the endoleak group received a Cook TX2 device (4 of 6; 66.67%) compared with other devices, one (16.67%) of Cook alpha and one (16.67%) of Medtronic Valiant. No patients receiving E-vita OPEN PLUS or the Terumo aortic developed endoleaks.

Table 2. Compared characteristics of the patients in both groups

	Endoleaks (n=6) (%)	**No endoleaks (n=20) (%)**
Prevalence	6/26 (23.08)	20/26 (76.92)
Age		
Mean ± SD	64.17 ± 5.78	70.10 ± 14.14
Median (IQR)*	63.5 (59.5 – 69.5)	73.5 (65 - 79)
Sex		
Male	4 (25.00)	12 (75.00)
Female	2 (20.00)	8 (80.00)
Hypertension	3 (16.67)	15 (83.33)
Diabetes mellitus	1 (16.67)	5 (83.33)
Dyslipidemia	3 (30.00)	7 (70.00)
Coronary artery disease	2 (40.00)	3 (60.00)
Renal insufficiency	1 (20.00)	4 (80.00)
Abdominal aortic aneurysm	1 (25.00)	3 (75.00)
length of follow-up (day)		
Mean ± SD	1251 ± 1069.36	622.85 ± 568.22
Median (IQR)	1337 (87 - 2329)	536 (45 - 141)

*p< 0.05 ; Mann-Whitney U test.

Table 3. Morphological characteristics of the aneurysm

	Total (n=26) (%)	**Endoleaks (n=6) (%)**	**No endoleaks (n=20) (%)**	***p*-value**
Morphology of aneurysm				0.999[(a)]
Saccular	16 (61.54)	4 (25.00)	12 (75.00)	
Fusiform	10 (38.46)	2 (20.00)	8 (80.00)	
Diameter of aneurysm(mm)				
Mean ± SD	61.69 ± 19.35	59.67 ± 20.99	62.3 ± 19.37	0.777[(b)]
Median (IQR)	62 (52.5 – 75.5)	60 (56 - 76)	62.5 (40 - 79)	
Length of the aneurysm (mm)				
Mean ± SD	72.62 ± 37.52	49.17 ± 16.29	79.65 ± 39.45	0.080[(b)]
Median (IQR)	67.5 (43.5 - 85.0)	53 (30.5 - 64.0)	76.5 (58 - 89)	

Table 3. Morphological characteristics of the aneurysm (Cont.)

	Total (n=26) (%)	Endoleaks (n=6) (%)	No endoleaks (n=20) (%)	*p*-value
Nature of aneurysm				0.999[(a)]
Pseudoaneurysm	1 (3.85)	-	1 (100.00)	
Post dissection	1 (3.85)	-	1 (100.00)	
Dissecting	2 (7.69)	-	2 (100.00)	
Degenerative	22 (84.62)	6 (27.27)	16 (72.73)	
Site of aortic aneurysm				0.999[(a)]
Descending	19 (73.08)	4 (21.05)	15 (78.95)	
Arch to descending	3 (11.54)	1 (33.33)	2 (66.67)	
Arch	4 (15.38)	1 (25.00)	3 (75.00)	

[(a)] Fisher's exact test. [(b)] Independent t-test. [(c)] Mann-Whitney U test.

Table 4. Peroperative conditions and technical considerations of TEVAR procedures

	Total (n=26) (%)	Endoleaks (n=6) (%)	No endoleaks (n=20) (%)	*p*-value
Type of procedure				0.644[(a)]
urgent	10 (38.46)	3 (30.00)	7 (70.00)	
elective	16 (61.54)	3 (18.75)	13 (81.25)	
LSA coverage	13 (50.00)	5 (38.46)	8 (61.54)	0.160[(a)]
Percent of oversizing proximal				
Mean ± SD	28.19 ± 11.81	35.17 ± 13.04	26.1 ± 10.90	
Median (IQR)	29.5 (19 - 39)	40 (21.5 - 44)	27 (17 - 33)	0.055[(c)]
Percent of oversizing distal				
Mean ± SD	33.69 ± 14.4	46.00 ± 16.26	30.00 ± 11.89	0.014[(b)]
Median (IQR)	33 (19.5 – 45.5)	49 (27.5 – 61.5)	29 (19 - 40)	
length of aortic coverage (mm)				
Mean ± SD	189.88 ± 85.68	193.33 ± 81.52	188.85 ± 88.91	
Median (IQR)	166 (150 - 216)	167.5 (137.5 - 275.0)	164.5 (150 - 216)	0.737[(c)]
Number of stent graft				0.697[(a)]
1	19 (73.08)	4 (21.05)	15 (78.95)	
2	6 (23.08)	2 (33.33)	4 (66.67)	
3	1 (3.85)	-	1 (100.00)	

Table 4. Peroperative conditions and technical considerations of TEVAR procedures (Cont.)

	Total (n=26) (%)	Endoleaks (n=6) (%)	No endoleaks (n=20) (%)	*p*-value
Type of stent graft				0.999[a]
Cook TX2	16 (61.54)	4 (25.00)	12 (75.00)	
Cook alpha	3 (11.54)	1 (33.33)	2 (66.67)	
Medtronic Valiant	4 (15.38)	1 (25.00)	3 (75.00)	
E-vita OPEN PLUS	2 (7.69)	-	2 (100.00)	
Terumo aortic	1 (3.85)	-	1 (100.00)	
Proximal landing zone (mm)				
Mean ± SD	50.12 ± 19.28	47.83 ± 17.49	50.8 ± 20.17	0.748[b]
Median (IQR)	51 (32.0 – 65.5)	46 (31.0 – 66.5)	52.5 (30 - 66)	
Distal landing zone (mm)				
Mean ± SD	53.73 ± 25.48	69.83 ± 35.93	48.9 ± 20.21	0.077[b]
Median (IQR)	49.5 (33.5 – 64.5)	57.5 (40.5 – 111.5)	47.5 (33 - 61)	

[a] Fisher's exact test. [b] Independent t-test. [c] Mann-Whitney U test

Postoperative conditions

All patients with endoleaks underwent reintervention (reintervention rate=100%). In addition, the open surgical conversion was performed to treat two patients (33.33%), including patients with type II (n=1) and type V (n=1) endoleaks with good outcomes. Endovascular techniques were successful in treating endoleaks among the remaining patients (n=4; 66.67%), using proximal (n=2) and distal (n=1) extensions for patients with type I endoleak, and RE-TEVAR with stent-in-stent was performed in one patient with endoleak type IV (n=1). Details of these remedial procedures are shown in **Table 5**.

All patients' mean changes in maximal aortic diameter were calculated by comparing the baseline aortic diameter with the maximal diameter at the last follow-up, irrespective of endoleak treatment. During follow-up, the median decrease of maximum aneurysm diameter among all patients with endoleaks was 21.5 mm, compared with 12.5 mm for those without endoleak as shown in **Table 6**. The median maximum aneurysm diameter decreased by 12 mm among patients with type I endoleak.

Table 5. Description of six patients with endoleaks, management and results

Endoleak patients	Type of endoleaks (n=6)	Onset of diagnosis after TEVAR (day)	Type of treatment	Result*
1	II	5	Ligation proximal LSA with repair left brachiocephalic vein	Successful
2	V	1881	Repaired Endoleak type V, pulmonary toilet and evacuation blood clot	Successful
3	IA	27	Proximal stent graft extension	Successful

Table 5. Description of six patients with endoleaks, management and results (Cont.)

Endoleak patients	Type of endoleaks (n=6)	Onset of diagnosis after TEVAR (day)	Type of treatment	Result*
4	IV	0.08	Re-TEVAR with stent-in-stent	Successful
5	IB	211	Distal stent graft extension	Successful
6	IA	98	Proximal stent graft extension	Successful

*Successful - Case of the endoleak who was resolved in the intraoperative angiography without any acute intra-operative complication.

Table 6. Maximum aneurysm diameter variations during follow-up in different types of patients with endoleak

Endoleak type	Decrease in sac diameter (mm)	*p*-value
No endoleak (n=20)		
Mean ± SD	18.4 ± 20.12	
Median (IQR)	12.5 (0.5 – 33.0)	
Endoleak (n=6)		0.502 (*)
Mean ± SD	22.83 ± 18.73	
Median (IQR)	21.5 (5 – 32)	
I (n=3)		
Mean ± SD	16 ± 13.45	
Median	12	
II (n=1)	52	
IV (n=1)	32	
V (n=1)	5	

(*) Mann-Whitney U test

Discussion

Endoleaks observed after endovascular repair have been well-described in the published data after EVAR, but few articles document their incidence and the consequences after TEVAR.[3] This series reports the prevalence of 23.08% of all types of endoleaks, which matches the range from 5 to 29% described in earlier series involving stent-graft repair of TAAs[8], and which is also similar to the endoleak incidence after EVAR.[8, 9]

The published data has described predictive factors of sac expansion after EVAR. Still, more is needed regarding the factors that predict endoleak development, especially after TEVAR.[4, 6] Related studies show that endoleak is a possible risk factor for TAA sac expansion after TEVAR.[4, 9, 10] On the contrary, in our study, patients without endoleak experienced lesser aneurysm sac regression than those with endoleaks (12.5 mm vs. 21.5 mm), although this difference was not statistically significant (p=0.5015). We recognize that our sample size was relatively small.

In our series, patients with endoleaks were significantly younger than those without endoleaks (p=0.041). Still, they had a wider age range in endoleaks than those in the nonendoleak group (range 56 to 74 vs. 27 to 87). In contrast, the study of Alsac et al. revealed that

older age significantly affected the occurrence of endoleaks. [4] Noisiri et al. and Belvroy et al. showed that mean ages were similar in the two groups.[10, 11] In other studies, the two groups were compared for age distribution; all patients with endoleaks presented a degenerative aneurysm.[8, 9] No difference was found in the prevalence of medical comorbidities between the two groups, compatible with prior studies.[8, 9] Corresponding with studies of Morales et al.[8] and Alsac et al.[4] the two groups did not differ in sex distribution, in contrast to Parmer et al.[6] showing that being male was a predictive factor of endoleaks.

Concerning the morphologic data of TAAs, no differences were noted between the two groups regarding maximum aneurysm diameter & length, morphology and location of the aneurysm, corresponding to the study findings of Noisiri et al.[10] Conversely, the study by Parmer et al. was the only study that reported the size of aneurysm sac significantly related with endoleaks.[9] Alsac et al. suggested that fusiform morphology was a factor of endoleaks.[4]

The most relevant morphologic factor associated with the incidence of endoleaks was the length of the proximal neck, that is, the distance between the LSA and the beginning of the descending thoracic aortic aneurysm (DTAA). The short proximal landing zone reflects the proximal character of the treated DTAA, which usually develops from the distal aortic arch and the proximal portion of the descending aorta. This portion of the thoracic aorta is known to be the worst landing zone because of its curvature,[12] leading to frequent mispositioning of the stent-graft and its inefficient proximal sealing.[13] Although we considered 20 mm as a minimum distance of the proximal landing zone,[14] this represented a significant issue in our series of TEVAR that could explain the large majority of proximal type I endoleaks among the endoleaks observed. On the other hand, in our study, the distance between the proximal and distal landing zone showed no difference between the two groups. Moreover, the left subclavian artery coverage, the diameter of graft at the proximal and distal aneurysm neck, and the length of aortic coverage showed no statistical significance between the two groups.

Among clinical variables, the percentage of graft oversizing over the aorta distal to the aneurysm among patients with endoleaks was significantly more than those among patients without endoleaks. The percentage of proximal graft oversizing in the endoleak group was also more than that in the non-endoleak group without statistical significance. These findings are based on experiences of EVAR in the abdominal aorta; stent-graft oversizing is essential, as it enhances the radial force of the device against the aortic wall, improving fixation and sealing. [15,16] On the other hand, excessive oversizing in EVAR is associated with an increased risk of complications. It may lead to infolding of the graft or dilatation of the aortic neck.[17] A systematic review of the influence of oversizing on the outcomes and complications in EVAR demonstrated 10 to 20% oversizing, corresponding to the Instructions of Use (IFU) of most manufacturers, offering the best results. [16] In contrast, the study base on TEVAR by Tolenaar et al. found the percentage of oversizing did not significantly affect the incidence of device-related complications after TEVAR for TAA.[18]

The type and the number of stent-grafts used were similar in both groups. A related study [4] found that Gore TAG was associated with endoleaks, but no such device has been used in our center. Currently, many up-to-date devices are available, which is better than in the past.

The mean decrease in maximum aneurysm diameter between the two groups showed no significant difference. Nonetheless, the related studies of Alsac et al. and Parmer et al. found that the persistence of an endoleaks led to significant sac expansion.[4, 6]

Although endoleaks after TEVAR were common in our series, no type III endoleak was reported. This could be explained using commercially available longer stent-grafts of up to 250 mm, allowing the deploying of only one graft in most procedures to obtain DTAA exclusion (1.3 stent-graft/patient). Moreover, lessons learned by the early implantations of stent-grafts of the first generation allowed us to understand the importance of a long overlapping zone between stent-grafts (>80 mm) when more

than one device was to be used to avoid later disconnection and type III endoleaks. [4] However, in a recent study, Noisiri et al. reported that the occurrence of endoleak type III was about 2.9%. [10]

All patients with endoleaks in our series underwent reintervention with successful results through type II endoleaks, which could be treated conservatively. In this study, the patient with unstable clinical history experienced type II endoleak repair. The result was similar to Noisiri et al. showing a success rate of 87.5%.[10]

The earlier series showed that predictive factors of endoleaks were bird beak configuration, landing zones 0 to 2, LSA coverage, large proximal neck and stent-graft diameters, excessive oversizing, aneurysm enlargement and length of the aneurysm. In the Thai population, factors that had statistically significant differences between patients with and without endoleaks were the landing zone and aortic arch for the aneurysm location.[10] In this study, younger age was also an associated factor of endoleaks, which was not a factor for predicting the decreased rate of aneurysm sac regression. The rate of reintervention and successful rate were also present in the study.

This study encountered limitations. The number of patients was relatively small, contributing to absolutely low numbers in each category. Regarding the small sample size; multivariable analysis to adjust the potential confounder was not performed. Additionally, the present study was conducted in only one hospital; the data may not represent the overall population. It will be interesting to perform a similar analysis on a cohort of patients in a multicenter study. Using CTA to diagnose and classify endoleaks in this study when diagnostic angiography is known to be more accurate [19] might have led to endoleak classification errors during radiologic follow-up.

Conclusion

Endoleaks after TEVAR is not a rare phenomenon, and their prevalence seems to be similar to that seen after EVAR. Patients at younger ages are at increased risk to develop endoleaks. The percentage of proximal graft oversizing over the aorta distal to the aneurysm among patients with endoleaks was significantly greater than those of patients without endoleak, corresponding to the IFU of most manufacturers, offering the best results. Type I endoleaks could be successfully treated using endovascular techniques with subsequent sac regression. The open surgical conversion was performed to treat patients with type II and type V endoleaks, and a hybrid procedure was successfully performed for type IV endoleaks. However, studies of higher sample sizes are further needed to assess the outcomes of other types of endoleaks.

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COMPARISON OF ANALGESIC EFFICACY BETWEEN ULTRASOUND -GUIDED ILIOHYPOGASTRIC/ILIOINGUINAL NERVE BLOCK AND WOUND INFILTRATION AMONG PATIENTS UNDERGOING GYNECOLOGIC SURGERY: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Postoperative pain control is essential after surgery to ensure early mobilization, decrease the length of hospital stay and provide patient comfort. Local anesthetic (LA) wound infiltration has been used to reduce postoperative pain. In addition, the bilateral iliohypogastric/ilioinguinal nerve block (IINB) has been used to control pain in abdominal surgery but not in gynecologic or pelvic surgery.

Objectives: This study aimed to evaluate the efficacy of ultrasound-guided iliohypogastric/ ilioinguinal nerve block compared with local anesthetic wound infiltration on postoperative pain control among patients undergoing gynecologic surgery through a Pfannenstiel incision**.**

Methods: In this prospective, double-blinded, randomized controlled trial, 50 patients were allocated to either an IINB group (N=25) or LA group (N=25). In both groups, postoperative IV patient-control analgesia (PCA) was planned 24 hours, postoperatively. The primary outcomes were differences in pain score using a numerical rating scale (NRS) and morphine consumption between both groups immediately following 2, 4, 8, 12 and 24 hours, postoperatively.

Results: The postoperative pain scores were significantly lower in the IINB group than in the LA group at all time points, with $p < 0.05$. Total morphine consumption for 2-24 hours postoperative was significantly lower in the IINB group than in the LA group with $p < 0.001$.

Conclusion: Compared with LA wound infiltration, this study demonstrated that IINB provided better pain control and reduced the consumption of morphine in the first 24 hours among patients undergoing gynecologic surgery through a Pfannenstiel incision.

Keywords: Iliohypogastric/ilioinguinal nerve block, Gynecologic surgery, Local anesthetic, Postoperative pain

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Introduction

The obstetrics and gynecologic surgeries with Pfannenstiel skin incisions are often associated with postoperative pain requiring a well-planned analgesic regimen to ensure early mobilization, decrease the length of hospital stay and provide patient comfort.[1] Any intervention that improves pain relief is worthy of investigation. Multimodal analgesics are often used to treat acute, postoperative pain. The systematic review of randomized trials has confirmed the analgesic efficacy of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors after surgery. They act on peripheral and central sites and interfere with pain mechanisms that differ from the opioid system. [2, 3]

The iliohypogastric/ilioinguinal nerves are parts of the lumbar plexus.[4] They provide sensation to the pubic area, lower abdomen, inguinal area, medial thigh, and genital organs. The IINB was performed by injecting an LA in the peripheral nerves to block any sensory signal to the spinal cord. It constitutes an effective technique, ensures safety, and reduces pain after surgery. This technique may be complex among patients with obese status and should be performed under an experienced anesthesiologist. The ultrasound-guided iliohypogastric/ilioinguinal nerve block has been increasingly used among patients for perioperative analgesia postabdominal surgery.[5-7] The iliohypogastric/ilioinguinal nerve block reduces opioid requirement, resulting in fewer opioid-mediated adverse effects and reduces the incidence of nausea and vomiting. This technique can reduce pain up to 12 hours postoperative. [8]

Local anesthetic wound infiltration is a common and easy technique to decrease postoperative pain in real-world practice. It involves injecting local anesthesia in the skin, subcutaneous tissue layer, and the surgical incision area, which can reduce pain up to 6 hours after surgery.[9] The authors hypothesized that the iliohypogastric/ilioinguinal nerve block provides superior postoperative pain relief than local anesthetic wound infiltration.

This study aimed to evaluate the efficacy of ultrasound-guided iliohypogastric/ilioinguinal nerve block compared with local anesthetic wound infiltration on postoperative pain control and amount of opioid consumption among patients undergoing gynecologic surgery using a Pfannenstiel incision.

Methods

A double-blinded randomized controlled trial was performed after approval by the Institutional Review Board of the Royal Thai Army Medical Department (ID: IRBRTA S084h/63). The thaiclinicaltrials.org registration number is TCTR20221205001. Written consent was obtained from all patients after receiving a comprehensive explanation of the possible risks and complications of nerve block. In addition, the potential risks and complications which could appear during the study were also explained.

All patients aged between 20 and 80 were scheduled for elective gynecologic surgeries under general anesthesia with endotracheal intubation at Phramongkutklao Hospital, Bangkok, Thailand. Patients were eligible for enrollment after categorizing as the American Society of Anesthesiologists (ASA) I to III and having good consciousness and communication ability. Exclusion criteria included patients with known allergy to bupivacaine, emergency surgeries, BMI $\geq$35 kg/m^2, renal impairment, liver impairment, known case chronic pain with potent opioids and inability to communicate with patients.

The sample size was calculated based on a related study by Sivapurapu et al.[10] A *p*-value less than 0.05 was considered significant at a power of 0.80. The number of anticipated patients was 22 in each group. Assuming a drop-out ratio of 10%, the sample size was 25 in each group.

Study design

From March 2021 to February 2022, a double-blinded randomized controlled trial study included patients scheduled for elective gynecologic surgeries for benign conditions such as total abdominal hysterectomy with or without bilateral salphingo-oophorectomy through a Pfannenstiel

incision; informed consent was obtained from 50 patients. General anesthesia with endotracheal intubation was performed in all cases. The baseline characteristics: age, BMI and the American Society of Anesthesiologists (ASA) category, were collected at the time of enrollment. **Figure 1** shows a CONSORT diagram of study participants (N= 50) meeting the inclusion criteria for the study. A computer-generated random number of randomized patients to either undergo iliohypogastric/ilioinguinal nerve block (IINB group) or receive local anesthetic infiltration in the surgical incision (LA group). The patients and investigators enrolling the patients were blinded to the intervention. On arrival at the operating room, patients were monitored using electrocardiogram, noninvasive blood pressure and pulse oximetry. All patients received a standardized induction of general anesthesia with fentanyl 1-2 µg/kg, propofol 1-2 mg/kg and cisatracurium 0.1 to 0.2 mg/kg. Endotracheal intubation was performed. Anesthesia was maintained using sevoflurane and 50% oxygen.

In the IINB group (N=25), the bilateral iliohypogastric/ilioinguinal nerve block was performed using an aseptic technique at the end of the operation by two regional anesthesia specialists and two trainees under the supervision of specialists. In the supine position, a linear ultrasound probe with high frequency (10 to 12 MHz) was placed obliquely along a line joining the anterior superior iliac spine (ASIS) and the umbilicus immediately superior and medial to the ASIS. In this location, the ilioinguinal and iliohypogastric nerves in between the transverses abdominus and internal oblique are defined as shown in **Figure 2**. The B Braun Stimuplex, a 22-gauge 80 mm needle, was inserted using an in-plane technique. The correct location of the needle tip is confirmed by an injection of 1 to 2 ml of normal saline to hydro-dissect the appropriate plane. After negative aspiration of blood, 20 ml of 0.25% bupivacaine was administrated in this plane. The procedure was repeated on the other side of ASIS to achieve a bilateral blockade.

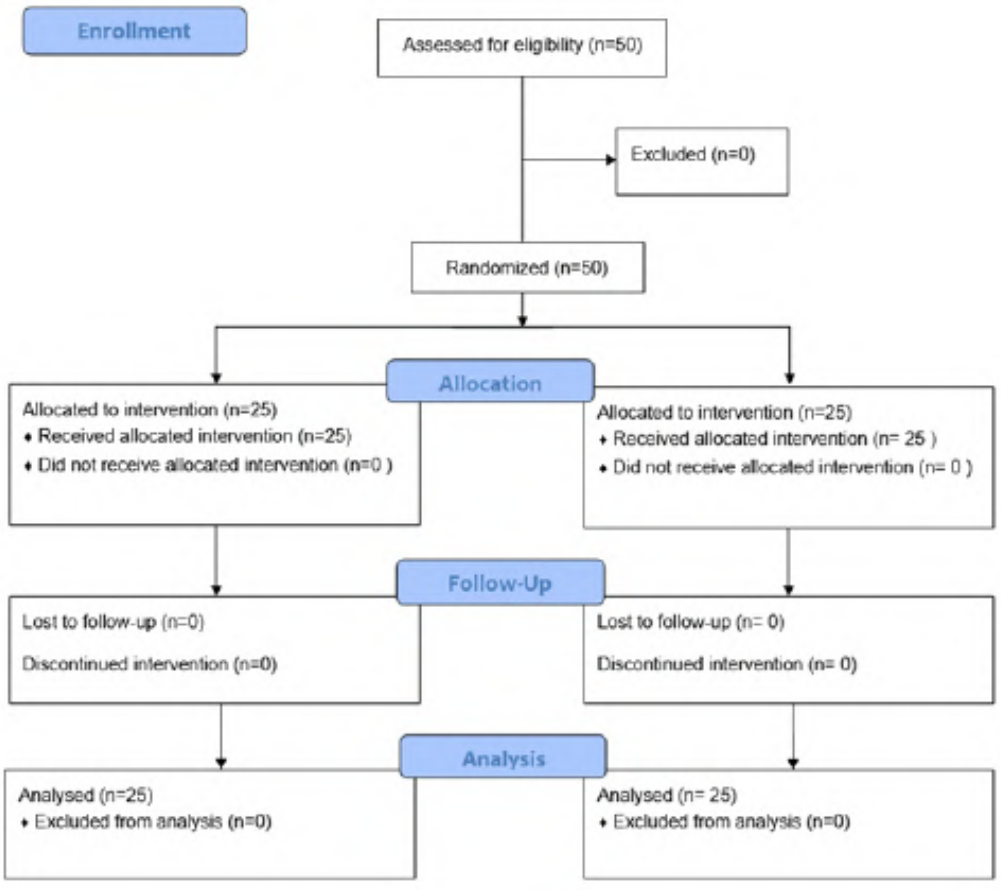

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram

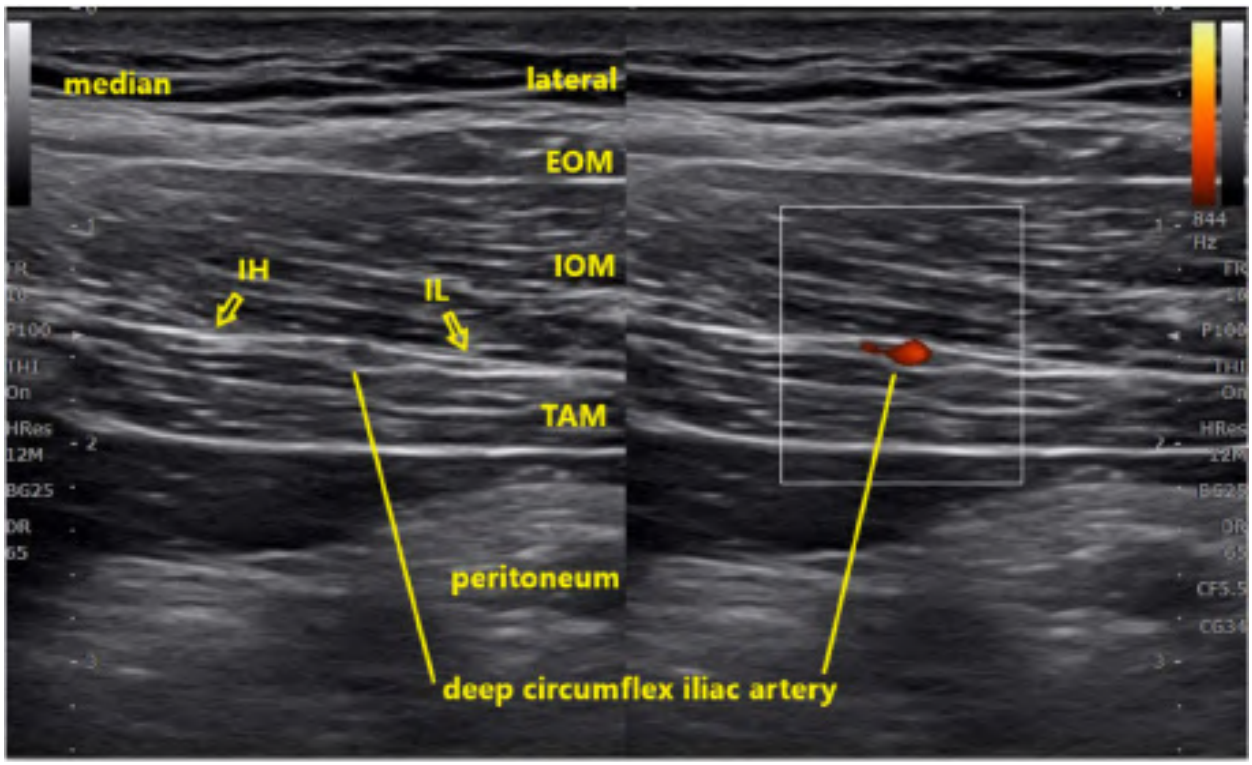

Figure 2. Ultrasound anatomy of the abdominal wall layers. EOM, external oblique muscle; IOM, internal oblique muscle; TAM, transverse abdominis muscle; IH, iliohypogastric nerve; and IL, ilioinguinal nerve

The LA group (N=25) was similar to the IINB group, under aseptic conditions. The surgeon administered the local infiltration with 20 ml of 0.5% bupivacaine at the end of the surgery. In addition, Ketorolac 30 mg and acetaminophen 1 g were administered intravenously to both groups 30 minutes before the end of surgery. All patients were connected to an intravenous patient-controlled analgesia (IVPCA) system. The PCA protocol was as follows: a loading bolus of 1 mg IV morphine, 1 mg for the subsequent bolus, followed by a lockout period of 5 min, with a maximal dosage of 20 mg within 4 hours. Patient-controlled analgesia continued 24 hours postoperatively. Additionally, the patients in both groups were given a postoperative analgesic regimen of injection ketorolac IV 30 mg 8 hourly up to 24 h.

At the end of the surgery, patients were awakened and taken to the recovery room. Postoperative pain scores using the Numerical Rating Scale (NRS, 0: no pain, 10: most severe pain to be estimated) and all parameters including adverse effects such as nausea, vomiting, hypotension, arrhythmia, pruritus and bradycardia, were assessed at 0, 2, 4, 8, 12 and 24 hours, postoperatively as shown in **Figure 3.** All data were collected by the same anesthesiologist blinded to the study group.

Statistical analysis

Statistical analysis was performed using computer software; STATA Statistical Software: Release 14. College Station, TX: StataCorp LP. The primary outcome was the difference in postoperative pain scores between the IINB and LA groups. The secondary outcome was the difference in morphine consumption in 24 hours postoperation between the IINB and LA groups. Demographic data were analyzed using an independent t-test and chi-square test. Pain scores (numerical rating scale), with paired comparisons at each time interval, were performed using the independent t-test. The 24-hour morphine requirement was analyzed using an independent t-test. The Shapiro-Wilks test was used to test the normality of data. Normally distributed data were presented as mean ± standard deviation (SD); $p < 0.05$ was considered statistically significant.

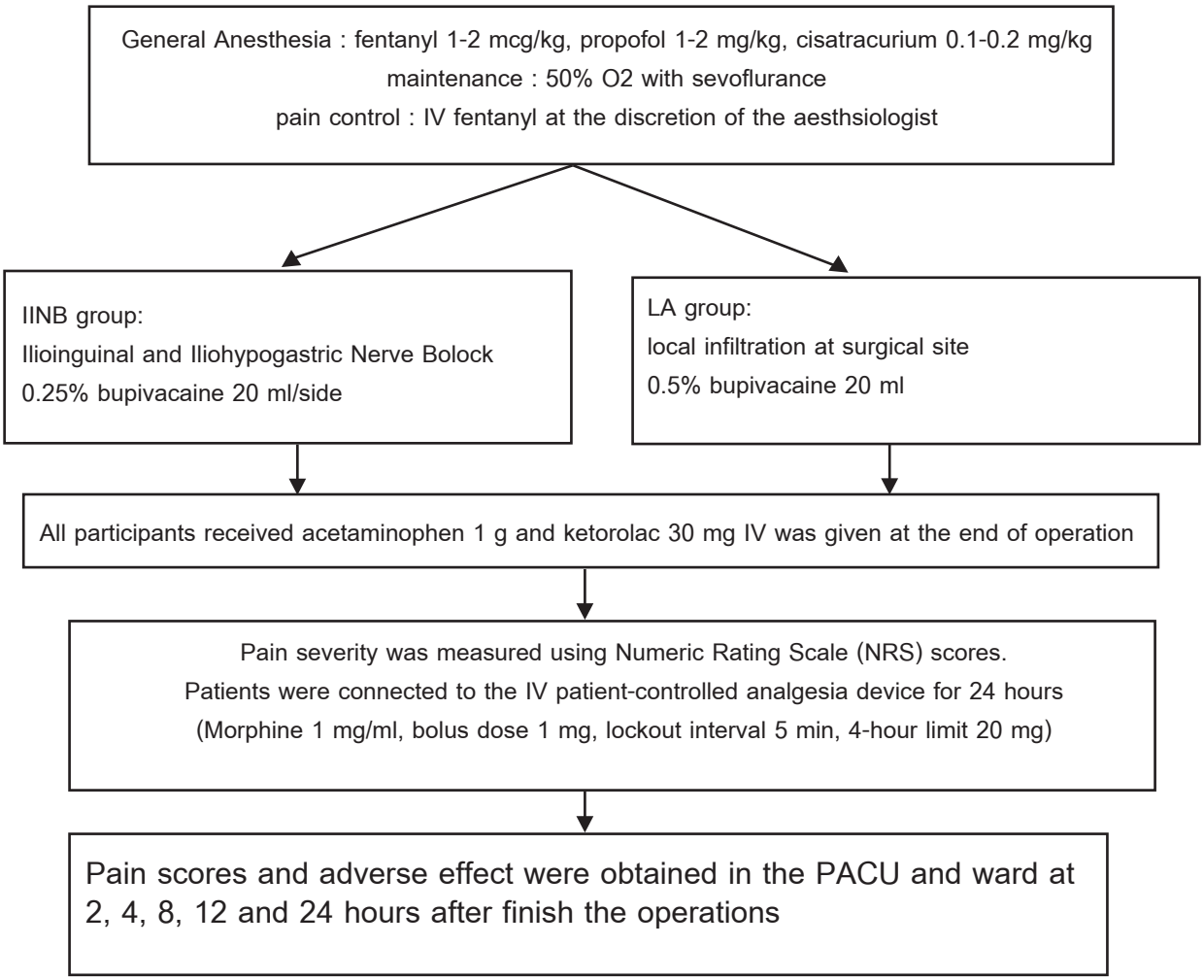

Figure 3. Flow chart represented method
IINB=iliohypogastric/ilioinguinal nerve block group, LA=local anesthetic wound infiltration group

Table 1. Demographic characteristics of the patients

Characteristics	IINB* (n=25)	LA# (n=25)
Age, yrs., mean (SD)	49.4 (4.2)	50.0 (4.2)
ASA**, number		
1	15 (60%)	9 (36%)
2	10 (40%)	16 (64%)
Weight, kg. mean (SD)	60.2 (6.9)	61.4 (7.9)
Height, cm. mean (SD)	158.3 (3.5)	158.6 (4.4)
BMI***, kg/m^2 mean (SD)	23.9 (2.2)	24.3 (2.3)

*IINB=iliohypogastric/ilioinguinal nerve block group, #LA=local anesthetic wound infiltration group,
**ASA=American Society of Anesthesiologists, ***BMI=body mass index., SD=standard deviation.
Pearson correlation coefficient, statistically significant at $p<0.05$

Results

A total of 50 randomized patients were recruited and allocated in two groups of 25 each. Both groups were comparable in the distribution of age, weight, height, body mass index (BMI) and ASA classification. No significant differences were noted regarding demographic data. All cases were benign and underwent transabdominal hysterectomy with or without bilateral salpingo-oophorecomy. The operative time was between 2 and 3 hours. **Table 1** summarizes the demographic characteristics of the patients.

Table 2. Postoperative pain scores of the iliohypogastric/ilioinguinal nerve block and local anesthetic wound infiltration groups at various postoperative time points

Postoperative time points (hour)	Pain score, mean (SD)		*p*-value
	IINB* n=25	LA# n=25	
0	4.8 (1.1)	6.7 (1.5)	<0.001
2	3.8 (0.7)	6.3 (1.4)	<0.001
4	2.9 (0.9)	5.4 (1.3)	<0.001
8	2.0 (1.0)	4.6 (1.3)	<0.001
12	0.8 (0.9)	3.2 (1.0)	<0.001
24	0.4 (0.6)	2.6 (0.6)	<0.001

*IINB=Iliohypogastric/ilioinguinal nerve block group, #LA=Local anesthetic wound infiltration group. Postoperative Numeric Rating Scale (NRS) scores. Independent t-test, statistically significant at $p<0.05$

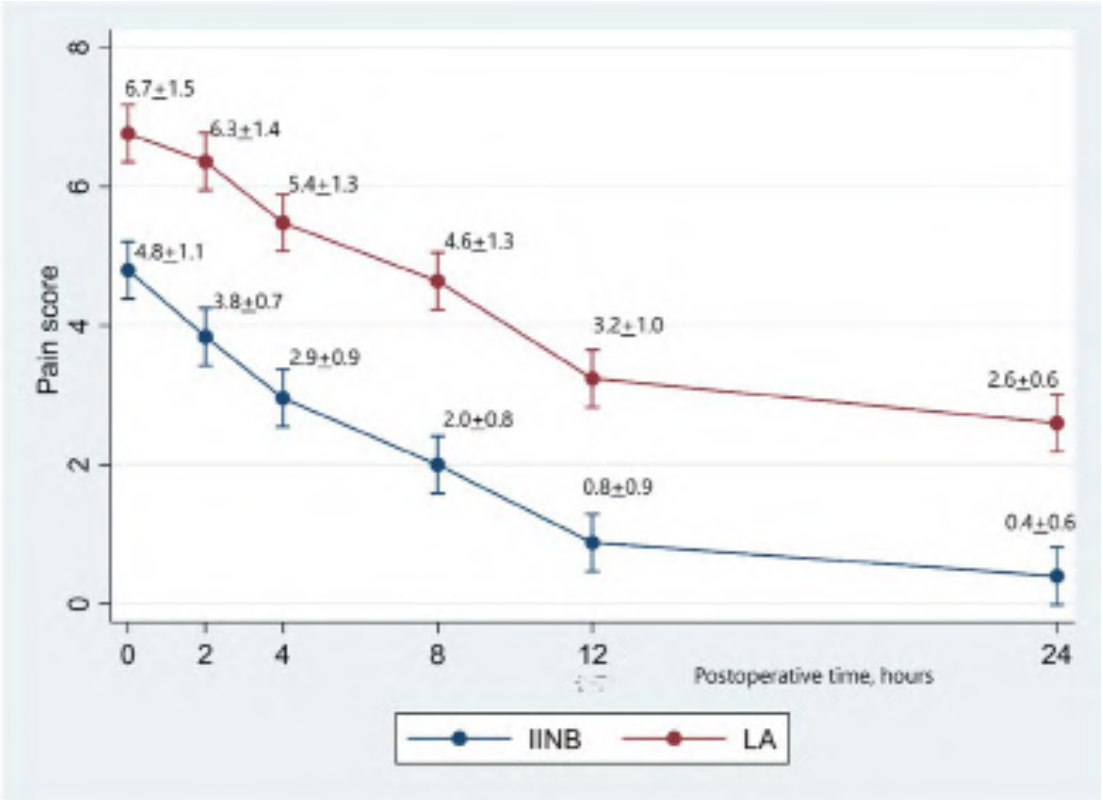

Figure 4. Postoperative pain scores of the iliohypogastric/ilioinguinal nerve block and local anesthetic wound infiltration groups at various postoperative time points
IINB=Iliohypogastric/ilioinguinal nerve block group,
LA=Local anesthetic wound infiltration group

The pain scores were significantly lower in the iliohypogastric/ ilioinguinal group than in the local anesthetic wound infiltration group at 0 hour (4.8±1.08 vs. 6.76±1.48), 2 hours (3.84±0.69 vs.6.37±1.38), 4 hours (2.96±0.93 vs. 5.48±1.29), 8 hours (2.0±1. vs. 4.64±1.29), 12 hours (0.88± 0.93 vs. 3.24±1.05) and 24 hours (0.4±0.65 vs. 2.6±0.65), postoperatively. (**Table 2, Figure 4)**

Table 3. Postoperative morphine consumption of the iliohypogastric/ilioinguinal nerve block and local anesthetic wound infiltration groups at various postoperative time points.

Postoperative time points (hour)	Morphine consumption (mg), mean (SD)		*p*-value
	IINB* n=25	LA# n=25	
0	0 (0)	0 (0)	N/A
2	3.5 (1.3)	6.3 (2.3)	<0.001
4	6.0 (1.6)	10.5 (4.1)	<0.001
8	7.8 (1.9)	13.3 (6.5)	<0.001
12	8.8 (2.5)	15.8 (7.2)	<0.001
24	9.2 (3.0)	18.4 (8.4)	<0.001

*IINB=iliohypogastric/ilioinguinal nerve block group, #LA=local anesthetic wound infiltration group, Independent t-test was statistically significant at $p<0.05$

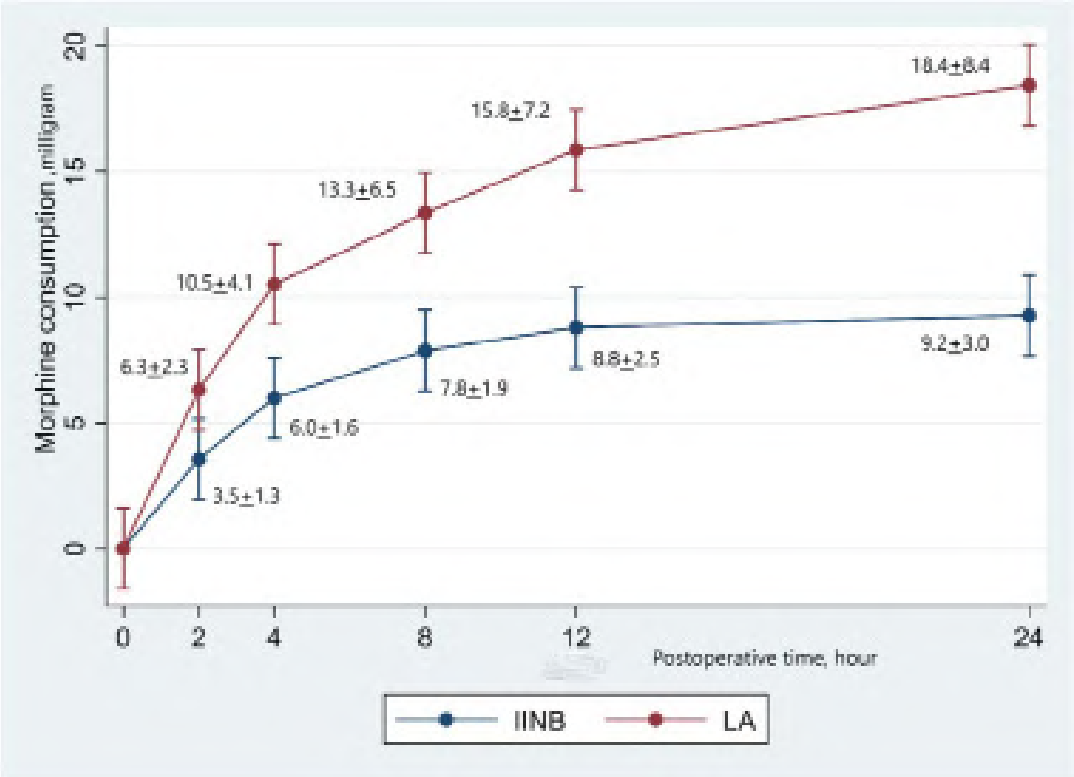

Figure 5. Postoperative morphine consumption of the iliohypogastric/ilioinguinal nerve block and Local anesthetic wound infiltration groups at various postoperative time points.
IINB=Iliohypogastric/ilioinguinal nerve block group,
LA=Local anesthetic wound infiltration group

Total morphine consumption is shown in **Table 3** and **Figure 5**. Consumption in the iliohypogastric/ilioinguinal group was lower than the local anesthetic wound infiltration group at 0, 2, 4, 8, 12 and 24 hours, postoperatively (p<0.05). Additionally, no reported cases of bleeding, swelling, or bruising at the iliohypogastric/ilioinguinal group injection site, nor were there episodes of excess sedation requiring medical review or removal of the PCA machine. Prophylaxis of postoperative nausea and vomiting with 8 mg ondansetron IV 30 minutes before the end of surgery was effective. No postoperative nausea, vomiting, or other adverse effects occurred among 50 patients.

Discussion

In this randomized, double-blind clinical trial, patients receiving bilateral iliohypogastric/ilioinguinal nerve blocks had significantly less postoperative pain and reduced morphine requirements compared with local anesthetic wound infiltration with bupivacaine. Local anesthetic wound infiltration is effective in postoperative pain management following obstetrics surgery with a Pfannenstiel incision. Still, in this study, the iliohypogastric/ilioinguinal nerve block appeared to be more effective. [9]

Pain in the postoperative period impedes recovery from surgery and anesthesia, and after gynecologic surgery through a Pfannenstiel incision, patients usually require strong analgesics for 24 to 48 hours. Potential analgesic methods include intraperitoneal, incisional or epidural injections of local anesthetics.[11] The iliohypogastric/ilioinguinal nerve block is another method at the time of a number of abdominal surgical procedures.[4-6]

The somatic or cutaneous pain from a Pfannensteil incision is principally conducted by the iliohypogastric and ilioinguinal nerves supplying afferent coverage to the L1-2 dermatome. The ilioinguinal nerve comprises fibers from the L1 nerve root with a contribution of fibers from the T12 nerve root in approximately 25% of patients.[12] Exiting from the lateral border of the psoas muscle, the ilioinguinal nerve follows a curvilinear course that takes it from the L1 and occasionally T12 somatic nerves to pass along the inside of the concavity of the ilium. The ilioinguinal nerve continues to pass anteriorly as it runs within a fascial plane between the internal oblique and transverse abdominis muscles. Within this fascial cleft the ilioinguinal nerve is identified with ultrasound scanning. At this point, the nerve is easily blocked using ultrasound-guided needle placement. [13]

In a related study, the efficacy of the transversus abdominis plane block and iliohypogastric/ilioinguinal nerve block in lower abdominal surgery was supported by randomized controlled trials.[14] On the contrary, a systematic review and meta-analysis demonstrated that transversus abdominis plane block did not significantly reduce morphine requirements compared with local anesthetic wound infiltration 24 hours after surgery. [15]

The local anesthetic is deposited in the plane between the internal oblique and the transverse abdominis muscle in the transversus abdominis plane block and the iliohypogastric/ilioinguinal nerve block. The ultrasound-guided iliohypogastric/ilioinguinal nerve block could target the ilioinguinal and iliohypogastric nerve more accurately and offers the advantage of direct visualization of the nerves and the adjacent anatomical structures.[4] Therefore, in this study, we chose an iliohypogastric/ilioinguinal nerve block to compare with local anesthetic wound infiltration.

Thus, the US-guided iliohypogastric/ilioinguinal nerve block is considered superior to local anesthetic wound infiltration, as proven by better pain relief scores and an opioid sparing analgesic efficiency. Moreover, the iliohypogastric/ilioinguinal nerve block easily achieved satisfactory quality ultrarasonographic visualization in the clinical setting. No adverse event occurred in this study in both group, similar to the related study. [16]

The study encountered several limitations. First, we did not record the intraoperative opioid consumption (intravenous fentanyl) and the last dose that might have affected the pain control postoperative period. Second, the study was performed on the postoperative pain score

and opioid use for only 24 postoperative hours. Third, the numeric rating pain scale was not objective, and there could have been some variability in the patient's ability to use this scale. Fourth, we did not perform pinprick or cold tests to determine sensorial block distribution to confirm the anesthetic level of the iliohypogastric/ilioinguinal nerve block. Lastly, this research was conducted at a training center in a single institution. Therefore, limitations were encountered regarding experienced anesthesiologists. It remains a not widely used technique in general hospitals.

Conclusion

The present study demonstrated that ultrasound-guided iliohypogastric/ilioinguinal nerve block achieved a comparably good analgesic effect and reduced morphine consumption in the first 24 hours after gynecologic surgery.

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Potential conflicts of interest

The authors declare they have no conflicts of interest.

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COGNITIVE FUNCTIONS AMONG PATIENTS WHO RECOVERED FROM COVID-19

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Abstract

Introduction: The Coronavirus disease 2019 (COVID-19) spread, causing a worldwide pandemic and affecting multiple organs and systems. The possible long-term sequelae of COVID-19 have become an increasing concern. Currently, little information exists about prolonged COVID-19 affects related to cognitive functions.

Objective: The study aimed to investigate the cognitive functions of patients who recovered from COVID-19 at least three months after the diagnosis.

Methods: A cross-sectional study was conducted to investigate cognitive functions among 150 employees of Buddhasothorn Hospital, Chachoengsao, Thailand. Of these, 75 employees had a history of COVID-19 at least three months after the diagnosis. Demographic characteristics were recorded and screened for depression, anxiety and insomnia. They were tested for their cognitive functions using the Montreal Cognitive Assessment (MoCA) and compared with 75 employees without a history of COVID-19.

Results: All postCOVID-19 cases presented mild COVID-19 symptoms. The results showed that 96% of COVID-19 in both groups, cases and the healthy group, had normal cognitive functions using the MoCA that did not significantly differ. However, the depression score in the postCOVID-19 cases was significantly higher than that of the participants without a history of COVID-19 (1.09 ± 1.36 and 0.61 ± 1.09, respectively (p = 0.018). Regression analysis between the postCOVID-19 cases and depression using multivariate analysis showed that the postCOVID-19 cases were associated with depression scale (β coefficient=0.470; 95%CI: 0.073, 0.867, respectively), after adjusting for age, sex, educational level and underlying diseases.

Conclusion: The cognitive functions of employees having a history of COVID-19 and without infection did not differ.

Keywords: Postacute COVID-19, Cognitive impairment, MoCA

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Introduction

In late 2019, the Coronavirus Disease 2019 (COVID-19) began to spread, causing a worldwide pandemic. Then March 11, 2020, the World Health Organization (WHO) announced that COVID-19 was a global public health problem.[1] COVID-19 could affect multiple organs and systems. Moreover, people who survived COVID-19 complained of a variety of symptoms. The most common symptoms reported were fatigue, headache, attention disorder, hair loss and dyspnea.[2-4] Consequently, the possible long term sequelae of COVID-19 have become an increasing concern. Likewise, to date, more information is needed about the long term sequelae of COVID-19. These studies also reported prolonged COVID-19-related cognitive impairment [5, 6] and unrelated cognitive functions.[7] We are interested in employees of the Buddhasothorn Hospital, Chachoengsao, because they gained a good education regarding COVID-19. Therefore, the present study aimed to investigate the cognitive functions of patients who had recovered from a COVID-19 at least three months after the diagnosis. The secondary objective was to study depression, anxiety and insomnia associated with COVID-19.

Methods

The study was approved and followed the Ethics principles of the Buddhasothorn Hospital (BSH-IRB number 015/2565). Between 1 September and 15 October 2022, a cross-sectional study was conducted among employees of a tertiary care hospital, the Buddhasothorn Hospital, Chachoengsao Province, Thailand. The participants were chosen using a purposive sampling technique from employees of the Buddhasothorn Hospital. Written informed consent was obtained from enrolled participants. We enrolled 75 employees who had recovered from COVID-19. All were confirmed positive for COVID-19 results using either a real-time polymerase chain reaction (RT-PCR) test or an antigen test kit (ATK) for COVID-19; participants were diagnosed at least three months beforehand. Next, 75 employees without a history of COVID-19 were enrolled. All participants were 18 to 60 years old, had not taken the Montreal Cognitive Assessment (MoCA) before and were free of depression, anxiety and insomnia.

The participants were interviewed for general personal information (sex, age, education and underlying diseases) and information about their COVID-19 illness (detection of the infection, severity of the symptoms and length of time of the symptoms). They were screened for depression and anxiety using the Thai Hospital Anxiety and Depression Scale (THAI HADS), [8] screened for insomnia using the Epworth Sleepiness Scale (ESS) [9] and tested for their cognitive functions using the MoCA.[10]

Assessment Tools

The MoCA Thai Version [10] is considered a measure for general cognitive impairment (visuospatial and executive functions, naming, attention, calculation, language, verbal abstraction, delay recall and orientation) assessed by a researcher trained in the evaluation of the test. The maximum MoCA score was 30 points (an additional point was given to a person with ≤12 years of education). The cut-off score for defining cognitive impairment was <25. The THAI HADS [8] was used to measure anxiety and depression, and the cut-off score was ≥11. The ESS [9] was used to measure, and the cut-off score was >10.

Statistics analysis

The baseline demographic and clinical characteristics of postCOVID-19 and healthy subjects were presented as frequencies or percentages and compared using the Chi-square or Fisher's exact tests, as appropriate. Continuous variables were presented as the means ± standard deviation (SD) (in the case of normal distribution), medians, and interquartile range, as appropriate. These were compared using the independent samples t-test and Mann-Whitney U test to correlate the mean score of the cognitive functions, anxiety, depression and daytime sleepiness.

To analyze the relationships among the dependent and independent variables including factors, cognitive functions, depression, anxiety

and insomnia, univariate and multivariate linear regression analyses were used. A two-sided α level of 0.05 was used for all tests**.**

Results

The demographic and clinical characteristics of the participants with and without a history of COVID-19 are shown in **Table 1**. The mean age, sex, level of education and underlying diseases did not significantly differ. They reported the following symptoms during the acute phase of the infection: cough (46.7%), anosmia (25.3%), fatigue (21.3%), dyspnea (17.3%), cognitive complaint (9.3%) and myalgia (8%). Additionally, the median duration of postCOVID-19 was two-weeks (IQR: 2 to 4).

Table 1. Demographics and clinical characteristics of participants with a history of COVID-19 and those without

Characteristic	Participants with a history of COVID-19 **(n = 75)**	Participants without a history of COVID-19 **(n = 75)**	***p*-value**
Age (years)	36.28 ± 10.49	36.97 ± 12.59	0.715[t]
Sex			
Female	65 (86.7)	66 (88.0)	0.806[c]
Male	10 (13.3)	9 (12.0)	
Education			
Primary school	0 (0.0)	2 (2.7)	0.279[f]
Secondary school	9 (12.0)	5 (6.7)	
Bachelor's degree or higher	66 (88.0)	68 (90.7)	
Underlying disease			
Yes	20 (26.7)	17 (22.7)	0.570[c]
No	55 (73.3)	58 (77.3)	
AR			
Yes	6 (8.0)	5 (6.7)	0.754[c]
No	69 (92.0)	70 (93.3)	
DM			
Yes	3 (4.0)	4 (5.3)	1.000[f]
No	72 (96.0)	71 (94.7)	
HT			
Yes	2 (2.7)	3 (4.0)	1.000[f]
No	73 (97.3)	72 (96.0)	
DLP			
Yes	1 (1.3)	1 (1.3)	1.000[f]
No	74 (98.7)	74 (98.7)	
Thyroid			
Yes	3 (4.0)	0 (0.0)	0.245[f]
No	72 (96.0)	75 (100.0)	
Others			
Yes	7 (9.3)	4 (5.3)	0.347[c]
No	68 (90.7)	71 (94.7)	

Table 1. Demographics and clinical characteristics of participants with a history of COVID-19 and those without (Cont.)

Characteristic	Participants with a history of COVID-19 (n = 75)	Participants without a history of COVID-19 (n = 75)	*p*-value
Covid-19 symptoms			
Anosmia	19 (25.3)		
Fatigue	16 (21.3)		
Dyspnea	13 (17.3)		
Cough	35 (46.7)		
Cognitive impairment	7 (9.3)		
Myalgia	6 (8.0)		
Other symptoms postCovid	3 (4.0)		
Duration of symptoms (weeks)	2 (2 - 4)		
Oxygenation	0 (0.0)		

Data were presented as a number (%), mean ± standard deviation or median (interquartile range). The *p*-value corresponded to the independent samples t-test, [m]Mann-Whitney U test, [c]Chi-square test, or Fisher's exact test.

The MoCA results of cognitive impairment among participants with and without a history of COVID-19 were equal to 4% each. The language score was significantly higher among participants with a history of COVID-19 than among those without a history (2.73 ± 0.53 postCOVID-19 patients; 2.48 ± 0.74 healthy controls; $p = 0.017$). Other scores did not significantly differ between the groups; the mean MoCA score was 27.75 ± 1.69 among participants with a history of COVID-19 and 27.36 ± 1.62 among those without ($p = 0.154$) (**Table 2**).

The mean anxiety scores of the THAI HADS among participants with a history of COVID-19 and those without were 2.04 ± 1.79 and 1.92 ± 1.73, respectively ($p = 0.677$). The mean score for doubtful cases (8 to 10) was 0.0% and 1.3%, respectively ($p = 1.000$). On the other hand, the mean depression score of the THAI HADS was significantly higher among participants with a history of COVID-19 compared with those without a history (1.09 ± 1.36 and 0.61 ± 1.09, respectively ($p = 0.018$)). (**Table 2**)

The mean scores of the ESS among participants with a history of COVID-19 and those without did not significantly differ for daytime sleepiness (3.17 ± 2.55 and 2.64 ± 2.74, respectively ($p = 0.219$)). The ESS scores among participants with and without a history of COVID-19 were 2.7 and 5.3%, respectively (**Table 2**).

Analysis of the relationship between post COVID-19 status and cognitive impairment, depression, anxiety and daytime sleepiness is shown in **Table 3.** The results of the regression analysis between postCOVID-19 status and cognitive impairment using univariate analysis and multivariate analysis showed that post-COVID-19 status had a statistically insignificant MOCA score (β coefficient = 0.387; 95% CI= -0.146, 0.919 and β coefficient = 0.381; 95%CI= -0.107, 0.868, respectively) after adjusting for age, sex, educational level and underlying diseases.

Regression analysis between the post-COVID-19 status and anxiety using univariate and multivariate analysis showed that post-COVID-19 status had no significant anxiety scale (β coefficient=0.120; 95% CI =-0.448, 0.688 and β coefficient=0.108; 95%CI: -0.455, 0.671, respectively), after adjusting for age, sex, educational level and underlying diseases.

Table 2. Comparison of the cognitive functions, anxiety, depression and daytime sleepiness between participants with a history of COVID-19 and those without

Characteristic	Participants with a history of COVID-19 (n = 75)	Participants without a history of COVID-19 (n = 75)	*p*-value
Montreal Cognitive Assessment (MoCA)			
Visuospatial/executive	4.85 ± 0.36	4.87 ± 0.34	0.815[t]
Naming	2.99 ± 0.12	2.97 ± 0.16	0.563[t]
Memory	1.00 ± 0.00	1.00 ± 0.00	NA
Attention	5.89 ± 0.35	5.89 ± 0.31	1.000[t]
Language	2.73 ± 0.53	2.48 ± 0.74	0.017[t]
Abstraction	1.95 ± 0.28	1.96 ± 0.26	0.761[t]
Delayed recall	3.36 ± 1.32	3.16 ± 1.27	0.347[t]
Memory index Score (MIS)	12.32 ± 2.34	11.68 ± 2.49	0.107[t]
Orientation	5.97 ± 0.16	6.00 ± 0.00	0.159[t]
MOCA score	27.75 ± 1.69	27.36 ± 1.62	0.154[t]
Cognitive impairment	3 (4.0)	3 (4.0)	1.000[f]
Anxiety	2.04 ± 1.79	1.92 ± 1.73	0.677[t]
Noncases (0-7)	75 (100)	74 (98.7)	1.000[f]
Doubtful cases (8-10)	0 (0.0)	1 (1.3)	
Depression	1.09 ± 1.36	0.61 ± 1.09	0.018[t]
Noncases (0-7)	75 (100)	75 (100)	NA
Epworth Sleepiness Scale	3.17 ± 2.55	2.64 ± 2.74	0.219[t]
Excessive daytime sleepiness (ESS score ≥10)	2 (2.7)	4 (5.3)	0.681[f]

The data were presented as a number (%), mean ± standard deviation or median (interquartile range). The P-value corresponded to the independent samples t-test, [m]Mann-Whitney U test, [c]Chi-square test, or Fisher's exact test.

Table 3 Multiple linear regression analysis for the association between COVID-19 with cognitive function, anxiety, depression and sleepiness

Outcome	B	(95%CI)	SE(B)	*p*-value
Univariate analysis				
MoCA Score	0.387	(-0.146, 0.919)	0.270	0.154
Anxiety subscale	0.120	(-0.448, 0.688)	0.287	0.677
Depression subscale	0.480	(0.083, 0.877)	0.201	0.018*
Epworth Sleepiness Scale	0.533	(-0.321, 1.388)	0.432	0.219
Multivariate analysis				
MoCA Score	0.381	(-0.107, 0.868)	0.247	0.125
Anxiety subscale	0.108	(-0.455, 0.671)	0.285	0.706
Depression subscale		(0.073, 0.867)	0.201	0.021*
Epworth Sleepiness Scale		(-0.321, 1.383)	0.431	0.220

Abbreviations: MoCA: Montreal Cognitive Assessment, B: β coefficient, SE(B): Standard error of B,
[a]Multiple linear regression model adjusted for age, sex, education and underlying disease
* Significant at $p < 0.05$

Regression analysis between postCOVID-19 status and daytime sleepiness using univariate and multivariate analysis showed that the post-COVID-19 status had a statistically insignificant Epworth sleepiness scale score (β coefficient= 0.533; 95%CI: -0.321, 1.388 and β coefficient = 0.531; 95%CI: -0.321, 1383, respectively), after adjusting for age, sex, educational level and underlying diseases.

On the other hand, regression analysis between postCOVID-19 status and depression using univariate and multivariate analysis showed that postCOVID-19 status was associated with depression scale (β coefficient = 0.480; 95% CI: 0.083, 0.877 and β coefficient = 0.470; 95% CI: 0.073, 0.867, respectively), after adjusting for age, sex, educational level and underlying diseases.

Discussion

This study showed that patients, who had recovered from a COVID-19 for at least three months, had the most common postCOVID-19 symptoms of cough, anosmia, fatigue, dyspnea, cognitive complaint and myalgia, which was similar to related studies.[2, 3] Furthermore, they had symptoms for about two weeks, similar to an earlier study by Tenforde et al.[11] Our studies were conducted on young patients with a mild COVID-19. They did not need oxygen therapy during the course of the infection; thus, leading to a quicker recovery. These symptoms were similar to postviral syndromes, such as influenza, Epstein-Barr virus and herpes.

The present study was conducted in a selected population of participants working in the Buddhasothorn Hospital. Therefore, the characteristics of the postCOVID-19 and healthy subjects did not differ regarding age, sex, educational level and underlying diseases. Both groups also had MoCA scores that did not significantly differ. [12-15] This result differed from related studies, possibly due to the population (age, degree of COVID-19, level of education and underlying diseases), neuropsychological assessment and design study. These related studies presented that postCOVID-19 status impaired cognitive functions such as executive function, attention, short term memory, language tasks and visuospatial processes. On the other hand, this study was similar to the related study of Mattioli et al.[7]Those participating in the study experienced a mild degree of COVID-19, obtained a high level of education and presented fewer comorbidities. This study showed that the language score in the postCOVID-19 group was higher than that of the healthy control, possibly due to excitement during the test. Some participants could follow the sentences correctly when consciously repeated, and they tended to lose points on the first test's sentence. Although the participants did not experience anxiety, depression or daytime sleepiness, the depression score of the THAI HADS in the post COVID-19 group was higher than that of the healthy control. This was similar to the related studies of Del Rio et al. [6] Mattioli et al. [7] and Woo et al.[14] reporting that patients who had recovered from COVID-19 experienced depression. Moreover, the results correlated between depression and MOCA score, which was known to affect cognitive impairment.

The main limitations of this research were a small sample size of studied subjects and mainly young patients with mild COVID-19 symptoms with a high education level. Therefore, analysis of large cohorts of patients with postCOVID-19 status could not be conducted. In addition, some risk factors of cognitive decline were not identified. However, to our knowledge, this constitutes one of the earliest studies in Thailand to investigate cognitive functions among patients who recovered from COVID-19. Further studies should be examine more neuropsychological and neuroimaging changes, which might yield more reliable results.

Conclusion

The results of this study demonstrated that cognitive functions amng young patients who had recovered from COVID-19 for at least three months after the diagnosis with mild COVID-19 symptoms did nodiffer from those without a history of COVID-19.

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EFFECT OF AGOMELATINE AND SERTRALINE ON SLEEP QUALITY AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE AND MAJOR DEPRESSIVE DISORDER: A DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Depression is a common comorbid disease among patients with chronic kidney disease (CKD). Insomnia, a symptom related to these conditions, negatively impacts disease progression and quality of life. Unfortunately, no consensus has been reached concerning treatment guidelines and choices of antidepressants suitable for treating depression among patients with CKD.

Objectives: The study aimed to evaluate the efficacy to sleep quality, depressive symptoms, safety and tolerability of agomelatine and sertraline in treating major depressive disorder among patients with CKD.

Methods: A double-blinded randomized controlled trial was conducted in the Nephrology Unit, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand. Patients with CKD and a diagnosis of major depressive disorder were randomly assigned to receive once-daily, fixed-dose sertraline 50 mg/d and agomelatine 25 mg/d. The treatment outcome was evaluated at 4 and 8 weeks. The Pittsburgh Sleep Quality Index score (PSQI) was used to measure sleep quality, and the Hamilton rating scale of depression, the Thai version (Thai HRSD-17), was used to evaluate depressive symptoms. Other outcomes included overall quality of life, side effects and tolerability.

Results: Agomelatine significantly improved sleep quality based on PSQI score throughout the observed period (p=0.002). Also, agomelatine more efficiently reduced depressive symptoms than sertraline (p=<0.001). In addition, patients receiving agomelatine as a treatment could continue their medication, whereas 52% of patients receiving sertraline discontinued because of side effects.

Conclusion: Agomelatine significantly improved sleep quality and tolerated well compared to sertraline.

Trial registration: thaiclinicaltrials.org ID: TCTR20200319005

Keywords: Chronic kidney diseases, Depression, Sleep quality, Clinical trial, Agomelatine, Sertraline

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Introduction

Major depressive disorder (MDD), defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[1] or subsyndromal depressive episode(s), is a common comorbidity among patients with chronic kidney disease (CKD). This mood disorder, combined with the burden of the medical conditions, affects many life aspects of the patients, such as the quality of life, the progression of the CKD and social support.[2-7] Both conditions impact the prognosis and treatment outcome of each other and directly affect the patients unless treated carefully.

Insomnia is one of the MDD symptoms. Poor sleep quality and a decrease in sleep time have a deteriorating impact on body functions and negatively affect the progression of CKD and MDD.[8, 9] Treating underlying causes usually relieves this symptom. However, therapeutic response in most classes of antidepressants occurs in approximately two to four weeks. During the initial period, benzodiazepines are commonly used as adjunctive treatment to reduce insomnia.[10, 11] Nevertheless, studies have indicated that using benzodiazepines among patients with CKD receiving kidney replacement therapy was associated with an increase in mortality rate[12, 13] constituting a complication caused by a treatment that should be focused on.

To achieve the best treatment outcome for this specific group, selecting antidepressants for treating MDD among patients with CKD should have an effect covering depressive symptoms, improving sleep quality, safety and good to lerability. Agomelatine is an atypical antidepressant with agonist action through melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2) and antagonist action through serotonergic receptor-type 2C (5-HT_{2C}). It has been hypothesized that agomelatine would affect circadian rhythm;[14] thus, reducing insomnia and enhancing sleep quality. A comparison study was conducted regarding the impact on sleep quality after being treated with agomelatine and sertraline, a standard treatment for MDD. The finding concluded that agomelatine improved the sleep quality of patients with MDD.[15] However,limited studies are available concerning using agomelatine among patients with MDD and comorbidity of CKD. Thus, this research aimed to determine the efficacy of agomelatine regarding sleep quality, depressive symptoms and tolerability in this specific group and compared with sertraline as a standard control treatment.

Methods

Study design

This comprised an 8-week, double-blinded, randomized control conducted at the Nephrology Unit, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand, from June 2019 to February 2020. The study was approved by the Ethics Committee of the Institutional Review Board, Royal Thai Army Medical Department and registered in thaiclinicaltrials.org (REF ID: TCTR20200319005).

The study population was allocated to one of two treatment groups: fixed-dose sertraline 50 mg/d, a standard treatment according to guidelines,[16] and fixed-dose agomelatine 25 mg/d, using block-of-four randomization and allocation concealment. All patients took one tablet once daily in the evening during the study period. The preparation of agomelatine and sertraline drugs employed the same package designs. Treatment outcomes were followed at four and eight weeks after starting the medications.

Study population

The study population consisted of patients with CKD stages 3 to 5, aged over 18. Patient Health Questionnaire-9 (PHQ-9) was used for screening patients with a risk of depressive disorder. Patients with PHQ-9 scores ≥7 were sent to meet a psychiatrist to examine and confirm their diagnosis. Patients with CKD stages 3 to 5 meeting the criteria of major depressive episode, according to DSM-5 and Hamilton Depression Rating Scale 17 items,

Thai version (Thai-HRSD17)[17] total score ≥8 were included. All participants had not received a diagnosis with major depressive episodes and were treatment-naïve to psychotropic medication, psychotherapy or brain stimulation therapy.

Patients with any of the following conditions were excluded: bipolar I or II disorder; obsessive-compulsive disorder; panic disorder; schizoaffective disorder or any other psychotic disorder; personality disorder; neurologic conditions; mild neurocognitive impairment; major neurocognitive disorder; alcohol or drug abuse or dependence within the past 12 months and risk of suicide. Additionally, patients were excluded if their medical conditions, confirmed by medical history, physical examination with laboratory investigation, were unstable, diagnosed with chronic pulmonary obstructive disease, end stage cancer, renal transplant, presented liver enzyme levels ≥3 times higher than the standard value, being pregnant or breastfeeding.

Efficacy of sleep quality

The Pittsburgh Sleep Quality Index (PSQI), Thai version [18, 19] was used to evaluate nocturnal sleep quality and sleep disturbance. This patient-rated questionnaire generates seven component scores: subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of the component scores yields one global score. A low total score implies better sleep quality and less sleep disturbance. Patients rated the questionnaire at the baseline, four and eight weeks.

Efficacy on depressive symptoms

The severity of depressive symptoms was measured using Thai-HRSD17 at the time of patient enrollment and followed at four and eight weeks. A significant reduction in Thai-HRSD17 score from the baseline assessment during the trial defined the efficacy of treatment on MDD.

Efficacy on quality of life

The overall change in the quality of life was assessed using the WHO quality of life brief measurement, Thai version (Thai WHOQOL-BREF). The 26-item, self-rated questionnaire measures an individual's perception in four domains of quality of life: physical, psychological, social relationship and environment. The improvement in quality of life was expressed as an increased score from baseline to the last postbaseline value.

Safety and tolerability

The side effects, safety and tolerability of each treatment were evaluated by patients' reports, and physical examinations during the fourth and eighth weeks of follow-up. The Antidepressant Side-effect Checklist (ASEC) was used as a guide for patients to identify their experience with side effects after taking medications. In addition, biological sampling and laboratory investigation were performed before randomly assigning patients to the treatment group and the eighth week of follow-up. Finally, a thorough evaluation was conducted in the case of withdrawal or ending medication for any reason.

Statistical analysis

All efficacies were performed according to intention-to-treat principles, defined as all patients receiving at least one dose of study medication, having at least one value at week 0 and at least one postbaseline value over the eight weeks was included in statistical analysis.

Descriptive statistical analysis was used to present the characteristics of each treatment group at baseline, including demographic data, sleep quality, the severity of depressive symptoms, and quality of life. Categorical data were presented as rate and percentage and continuous data were presented as mean with standard deviation. The chi-square or Fisher's exact test was used to examine possible differences in categorical variables. In addition, the Independent t-test or Mann-Whitney U test was used to identify differences between continuous outcomes.

Analysis of variance (ANOVA) was used to determine the differences in treatment outcomes from baseline to postbaseline at four and eight weeks. One-way repeated measure ANOVA was used to compare results in the same treatment group, and two-way repeated measure ANOVA was used to compare outcomes between different treatment groups. Statistical significance was accepted as $p<0.05$.

Results

Patients

Of 53 patients with CKD recruited in this clinical trial, 26 patients were randomly assigned to the fixed-dose sertraline 50 mg/d treatment group, and the other 27 patients were assigned to the fixed-dose agomelatine 25 mg/d group. Two patients from each treatment group were lost to follow-up. Thus, 25 patients in the sertraline group and 26 patients in the agomelatine group were included in the analysis. A comparison of the demographic and clinical data of the patients is presented in **Table 1**. No statistically significant difference between groups was observed among the 27 females (52.9%) and 24 males (47.1%). The average age of the patients was 64 years. Most patients had chronic kidney disease stage 5 with an average estimated glomerular filtration rate (eGFR) of 11.34 ml./minute/1.73/m^2. Altogether, 24 patients (47.1%) received kidney replacement therapy.

Table 1. Comparison of the demographic and pretreatment clinical data

	Total (51) n (%)	Sertraline (25) n (%)	Agomelatine (26) n (%)	*p*-value
Sex				0.322
Male	24 (47.1)	10 (40.0)	14 (53.8)	
Female	27 (52.9)	15 (60.0)	12 (46.2)	
Age (year); Mean ± SD	64.04 ± 13.61	65.37 ± 13.81	62.76 ± 13.57	0.499‡
Body mass index (kg./ sq.m.); Mean ± SD	24.16 ± 5.14	23.37 ± 4.93	24.91 ± 5.32	0.311‡
CKD stage				0.630†
stage 1	-	-	-	
stage 2	-	-	-	
stage 3a	5 (9.8)	1 (4.0)	4 (15.4)	
stage 3b	10 (19.6)	6 (24.0)	4 (15.4)	
stage 4	8 (15.7)	4 (16.0)	4 (15.4)	
stage 5	28 (54.9)	14 (56.0)	14 (53.8)	
eGFR; Median (Min - Max)	11.34 (3.98 - 51.70)	12.9 (3.98 - 49.71)	9.78 (4.21 - 51.7)	0.348¥
Kidney replacement therapy				0.488
No	27 (52.9)	12 (48.0)	15 (57.7)	
Yes	24 (47.1)	13 (52.0)	11 (42.3)	
Kidney replacement therapy method				0.598†
None	27 (52.9)	12 (48.0)	15 (57.7)	
Hemodialysis	21 (41.2)	12 (48.0)	9 (34.6)	
CAPD	3 (5.9)	1 (4.0)	2 (7.7)	

Table 1. Comparison of the demographic and pretreatment clinical data (Cont.)

	Total (51) n (%)	Sertraline (25) n (%)	Agomelatine (26) n (%)	*p*-value
Sleep quality; Mean ± SD				
Global PSQI		12.12 ± 3.13	12.31 ± 4.26	0.859‡
Subjective sleep quality		1.80 ± 0.82	1.88 ± 0.99	0.742
Sleep latency		1.92 ± 1.19	2.27 ± 1.08	0.277
Sleep duration		2.12 ± 1.17	2.27 ± 0.96	0.620
Habitual sleep efficiency		2.4 ± 1.12	2.15 ± 1.19	0.450
Sleep disturbance		1.44 ± 0.51	1.73 ± 0.72	0.104
Use of sleep medication		1.16 ± 1.31	0.85 ± 1.26	0.387
Daytime dysfunction		1.28 ± 0.61	1.15 ± 0.73	0.509
Severity of depressive symptoms; Mean ± SD		22.72 ± 4.16	24.46 ± 5.05	0.186
Quality of life; Mean ± SD		70.36 ± 9.75	70.12 ± 11.3	0.934

Chi-square test, †Fisher's exact test, ‡Independent t-test, ¥Mann-Whitney U test,
** Significant if $p<0.05$
Abbreviation: CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate

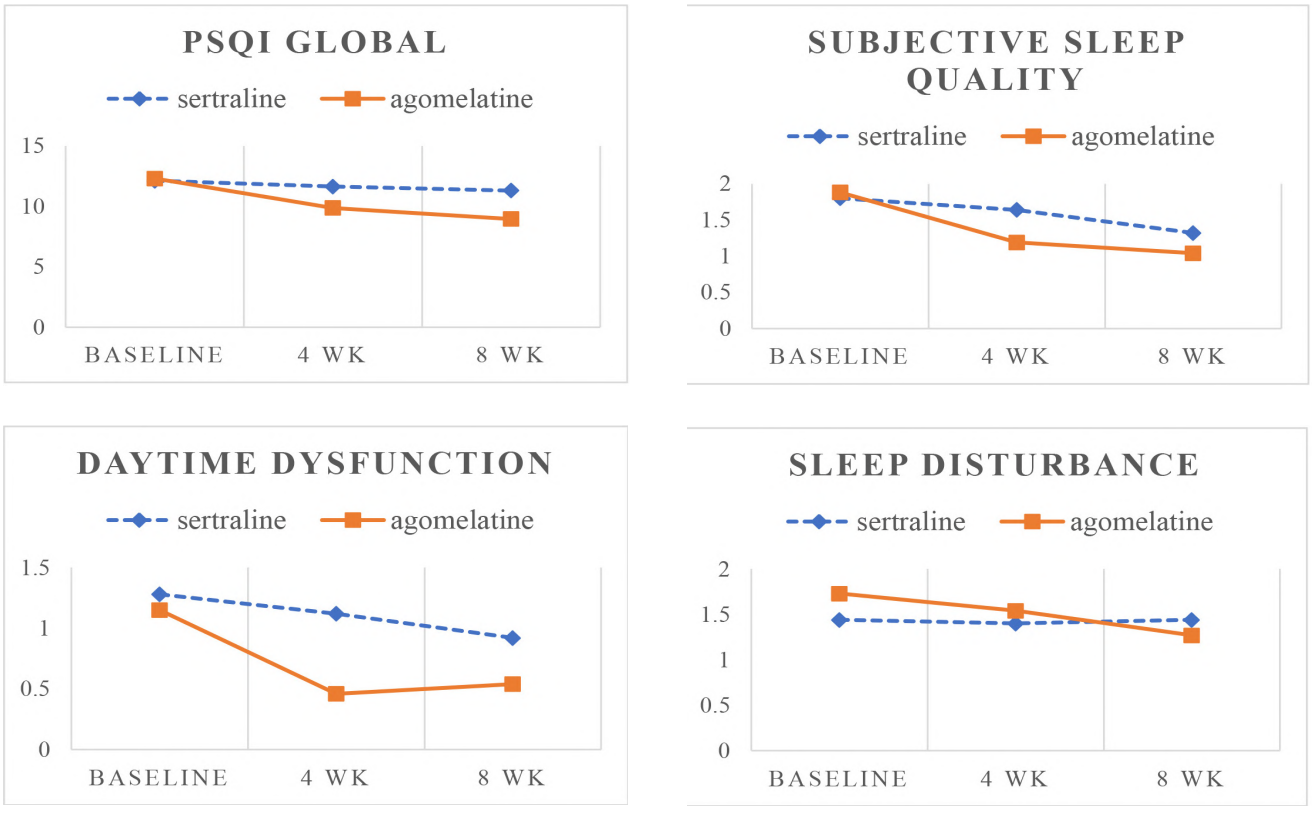

Figure 1. Change in sleep quality

Table 2. Improvement of sleep quality

	n	Baseline Mean±SD	4 weeks Mean±SD	8 weeks Mean±SD	*p*-value
PSQI global					
Sertraline	25	12.12 ± 3.13	11.64 ± 3.96	11.32 ± 4.43	0.497
Agomelatine	26	12.31 ± 4.26	9.88 ± 4.14	8.96 ± 4.36	0.002**
PSQI component 1 - Subjective sleep quality					
Sertraline	25	1.80 ± 0.82	1.64 ± 0.81	1.32 ± 0.8	0.018**
Agomelatine	26	1.88 ± 0.99	1.19 ± 0.94	1.04 ± 0.77	0.001**
PSQI component 2 - Sleep latency					
Sertraline	25	1.92 ± 1.19	2 ± 0.91	1.92 ± 1.15	0.878
Agomelatine	26	2.27 ± 1.08	1.88 ± 1.24	1.88 ± 1.18	0.130
PSQI component 3 - Sleep duration					
Sertraline	25	2.12 ± 1.17	1.96 ± 1.17	2.04 ± 1.17	0.460
Agomelatine	26	2.27 ± 0.96	2.15 ± 1.01	1.73 ± 1.15	0.066
PSQI component 4 - Habitual sleep efficiency					
Sertraline	25	2.40 ± 1.12	2.28 ± 1.21	2.36 ± 1.04	0.881
Agomelatine	26	2.15 ± 1.19	1.96 ± 1.4	1.85 ± 1.38	0.499
PSQI component 5 - Sleep disturbance					
Sertraline	25	1.44 ± 0.51	1.4 ± 0.5	1.44 ± 0.58	0.929
Agomelatine	26	1.73 ± 0.72	1.54 ± 0.65	1.27 ± 0.45	0.001**
PSQI component 6 - Use of sleep medication					
Sertraline	25	1.16 ± 1.31	1.24 ± 1.42	1.32 ± 1.35	0.872
Agomelatine	26	0.85 ± 1.26	0.69 ± 1.23	0.65 ± 1.2	0.671
PSQI component 7 - Daytime dysfunction					
Sertraline	25	1.28 ± 0.61	1.12 ± 0.83	0.92 ± 0.86	0.167
Agomelatine	26	1.15 ± 0.73	0.46 ± 0.58	0.54 ± 0.76	0.001**

One-way repeated measures ANOVA
** Significant if $p < 0.05$
Abbreviation: PSQI – Pittsburgh sleep quality index

Sleep quality (**Table 2**) (**Figure 1**)

No clinical difference was noted in sleep quality between each group at pretreatment (**Table 1**). However, following up at four and eight weeks after treatment, both groups showed declining global PSQI scores implying better sleep quality. When observing the change of global score at different time points in the same treatment group, fixed-dose agomelatine 25 mg/d showed a statistically significant improvement in sleep quality; conversely, fixed-dose sertraline 50 mg/d showed no drastic change. However, when comparing the efficacy in improving sleep quality between agomelatine and sertraline, no significant difference was observed.

In the case of component scores of PSQI, agomelatine significantly provided better subjective sleep quality, decreased sleep disturbance and decreased daytime dysfunction, while sertraline only showed improvement in personal sleep. Furthermore, comparing the medications, agomelatine exhibited a more significantly reduced daytime dysfunction than sertraline (two-way repeated ANOVA, $p = 0.008$).

PSQI global and some subcomponent scores in the agomelatine group significantly declined throughout the treatment period. In contrast, PSQI and subcomponent scores (except subjective sleep quality) in the sertraline group showed an insignificant decline.

Depression and quality of life (**Table 3**) (**Figure 2**)

After using the medications, the HRSD-17 scores of both treatment groups declined from baseline. Although improved depressive symptoms could be observed in both groups, Surprisingly, sertraline showed no clinically significant change in depressive symptoms. Only agomelatine significantly reduced depressive symptoms when comparing scores from baseline to posttreatment within the treatment group. This results in agomelatine significantly reduced depressive symptoms than sertraline (two-way repeated ANOVA, $p < 0.001$).

The overall quality of life in the agomelatine group improved compared with the baseline value. When compared with the sertraline group, the overall quality of life in the agomelatine group was better with statistical significance. (two-way repeated ANOVA, $p < 0.001$).

Safety and tolerability

ASEC is a self-reported instrument to identify 21 common side effects, including dry mouth, drowsiness, difficulty sleeping (insomnia),

Table 3. Improvement of depressive symptoms and quality of life

Severity of depressive symptoms (HRSD-17)					
	n	**Baseline Mean±SD**	**4 weeks Mean±SD**	**8 weeks Mean±SD**	***p*-value**
Sertraline	25	22.72 ± 4.16	22.56 ± 8.75	18.96 ± 10.8	0.149
Agomelatine	26	24.46 ± 5.05	11.27 ± 5.5	10.23 ± 5.79	<0.001**
Quality of life (WHOQOL-BREF)					
	n	**Baseline Mean±SD**	**4 weeks Mean±SD**	**8 weeks Mean±SD**	***p*-value**
Sertraline	25	70.36 ± 9.75	71.24 ± 14.37	73.92 ± 14.76	0.471
Agomelatine	26	70.12 ± 11.3	83.46 ± 9.30	80.96 ± 15.92	<0.001**

One-way repeated measures ANOVA

** Significant if $p < 0.05$

Depression and quality of life, measured by HRDS and WHO-Qol-BREF, significantly improved in the agomelatine group.

Abbreviation: HRSD – Hamilton rating scale for depression, WHOQOL-BREF – WHO quality of life BREF

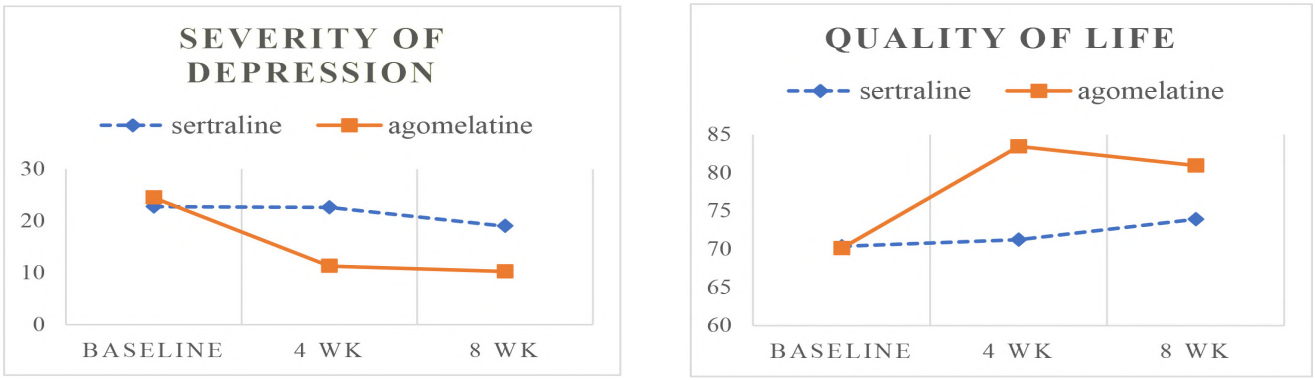

Figure 2. Change in depressive symptoms and quality of life

blurred vision, headache, constipation, diarrhea, increased appetite, decreased appetite, nausea or vomiting, problems with urination, problems with sexual function, palpitations, feeling light-headed on standing (orthostatic dizziness), feeling like the room is spinning round (vertigo), sweating, increased body temperature, tremor, disorientation, yawning and weight gain. Each item in the instrument also measures the severity of side effects ranging from absent to high. Common side effects reported from both groups after taking medication were dry mouth, nausea/vomiting, headache and drowsiness. The severity of symptoms was milder in agomelatine than in sertraline. Neither severe side effects nor death was found. Adverse drug reactions were generally less frequent in the agomelatine group than in the sertraline group (nausea/vomiting: 3.85 vs. 64%; dry mouth: 15.38 vs. 44%; and headache: none in agomelatine vs.20%). Only drowsiness was more common in the agomelatine group than in the sertraline group (15.38 vs. 2%).

Of 25 patients taking sertraline, 13 patients (52%) stopped taking medication before the complete follow-up visit at eight weeks. Intolerable side effects were the main reason. In contrast, only one patient (3.85%) from the agomelatine group stopped taking medication. Following the intention-to-treat protocol, all patients receiving medication at least once and completely followed up were included in the analysis.

Discussion

MDD is highly prevalent among patients with CKD. The co-occurrence of both diseases affects each other, reducing the quality of life and complicating management[20-22]. Burdened by either one of these conditions or both, patients are more susceptible to insomnia, further accelerating disease progression and negatively impacting the quality of life. To improve treatment outcomes, proper management of insomnia and depression under CKD became our focus.

Several physiological changes associated with CKD were proposed to be factors causing insomnia. Circadian sleep-wake cycle disruption was one of the possible causes. Evidence indicates that the nocturnal releasing of melatonin, a hormone involved in circadian rhythm, decreased with deteriorating renal function and conventional daytime hemodialysis did not correct or improve melatonin secretion.[23-26] Sleep regulation is also impaired in MDD. Thus, the medication that can restore circadian rhythm might have more significant benefits in improving sleep quality. As a result of this study, agomelatine revealed significantly improved overall sleep quality. Better subjective feelings of sleep, decreased sleep disturbances and reduced daytime dysfunction are associated factors of improved sleep quality. Sertraline shows minimal improvement in subjective sleep feeling but without significantly changing overall sleep quality. The finding is in line with other studies,

reflecting improvement with agomelatine when compared with SSRIs.[27-29] The antagonist action to the 5-HT_{2C} receptor along with the agonist action to MT1 and MT2 of agomelatine may contribute to the correction of the disrupted circadian rhythm found among patients with depression and chronic kidney disease; thus, enhancing sleep quality.[2, 23, 8-30] However, the improved sleep quality from agomelatine was not statistically significant compared with sertraline in this study. This may have been caused by the small sample size and duration of observation; therefore, not yielding a clear difference.

Regarding efficacy on depressive symptoms, all antidepressants were effective in reducing severity compared with placebo in the general population. Minor differences were found in treatment efficacy between each antidepressant, and the distinction of each antidepressant depended on side effects and tolerability.[31] Several antidepressants have been recommended for depression among patients with advanced-stage CKD.[32, 33] However, recent evidence proved that no significant improvement occurred in depressive symptoms among patients with CKD when compared with antidepressants with placebo or psychological interventions.[34-36] In this regard, the choices of antidepressants among patients with MDD-CKD should not be limited only to efficacy but also consider tolerable side effects and quality of life. From this study, agomelatine exhibited a promising result. Depressive symptoms remarkably decreased, and overall quality of life improved among patients with MDD-CKD assigned to the agomelatine group. However, sertraline failed to ameliorate depressive symptoms and improve quality of life. The probable reason supporting these outcomes was that patients with MDD-CKD in the sertraline group were more likely to stop taking medications. Patients taking sertraline experienced more adverse drug reactions with moderate to high severity. Thus, many patients cannot adhere to the medication, resulting in treatment failure. The patients taking agomelatine experienced mild side effects after starting the medication. The degree of adverse drug reactions correlated with the tolerability of medication and treatment adherence. Patients with CKD may be more sensitive to medication side effects due to changes in their body metabolism and renal excretion.

This study encountered limitations, including a small number of enrolled subjects and a short duration of result observation. Additionally, the focus of this study was sleep quality among patients with MDD-CKD rather than depression. Therefore, the dosage of antidepressants was not adjusted in proportion to the severity of depressive symptoms and treatment response. Furthermore, the sleep quality in advanced-stage CKD should be cautiously evaluated due to factors that could disturb sleep other than MDD, such as uremia, volume status or other medical conditions. Finally, patients with MDD-CKD in this study were treated in the outpatient department and excluded patients with suicidal thoughts. These all limit the generalizability of the findings.

Conclusion

Agomelatine showed a favorable effect on sleep quality and modest side effects. Although agomelatine did not demonstrate a significant efficacy over sertraline, agomelatine can be a treatment choice for treating depression and insomnia among patients with CKD. Although limited by the small sample size, the results show promising outcomes that agomelatine has better efficacy and is more tolerable than sertraline in this particular population.

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Declaration of interest

The authors report no other conflicts of interest in this work.

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COMPARISON OF THE EFFECTIVENESS OF REMDESIVIR VERSUS FAVIPIRAVIR ON CLINICAL IMPROVEMENT AND MORTALITY AMONG PATIENTS WITH COVID-19 PNEUMONIA: A RETROSPECTIVE SINGLE-CENTER STUDY

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Abstract

Background: Antiviral drug administration in the early phase of COVID-19 during peak viremia can reduce the progression to severe disease. The optimal antiviral treatment against severe coronavirus disease 2019 (COVID-19) has not been proven.

Objective: The study aimed to examine the effectiveness of remdesivir versus favipiravir to treat patients with COVID-19 pneumonia on clinical improvement and mortality.

Methods: This retrospective observational cohort study was conducted in the modular intensive care unit and cohort ward from 1 June 2021 to 31 December 2021. Patients were screened for COVID-19 pneumonia. A propensity score was used to handle selection bias and potential confounding factors. The propensity score estimation was obtained from the multivariable logistic regression model, including prognostic covariates. Then 1:1 matching was performed. Finally, the balance after matching was checked concerning the *p*-value.

Results: Overall, 362 patients were matched using propensity score analysis; they were enrolled and divided in 2 groups: remdesivir and favipiravir (181:181). Remdesivir was associated with an increased proportion of clinical improvement (70.72 vs. 56.91%, adjusted HR=1.52 [1.16-2.01]; p=0.002), reduced inhospital mortality (adjusted HR=0.68 [0.47-0.99]; p=0.047), an increased proportion of being free from the use of a high flow nasal cannula (HFNC) and a low flow oxygen cannula (LFNC) (74.34 vs. 56.10%, adjusted HR 1.79 [1.32-2.45]; p<0.001; 86.4% vs. 74.8, adjusted HR=1.34 [1.01-1.78]; p=0.037, respectively), increased median survival time (26 vs. 24 days, median survival time difference of 2 days [IQR, 2-6]; p=0.048). In addition, patients treated with remdesivir showed a significantly higher proportion of discharge from the hospital measured using the WHO ordinary scale (66.85 vs. 53.04%, adjusted HR =1.19 [1.01-1.41]; p=0.035).

Conclusion: Among hospitalized patients with COVID-19 pneumonia, receiving oxygen supplementation, remdesivir was associated with increased clinical improvement, reduced in-hospital mortality and reduced need for HFNC and LFNC.

Keywords: COVID-19, Remdesivir, Favipiravir, Effectiveness, Mortality, Clinical improvement
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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), was first reported in China and has spread worldwide. In Thailand, COVID-19 began to spread in Bangkok in May 2020 and affected many provinces nationwide. As a result, Thailand recorded 2,361,702 patients and 22,000 deaths (data as of January 21, 2022), with the highest number of daily deaths reported August 18, 2021, at 312.[1] Reducing the infection rates, deaths or severe illness is important.

SARS-CoV-2 causes severe acute respiratory syndrome, and may require hospitalization. Morbidity and mortality are linked to several factors, such as age and coexisting medical conditions. Efforts have been made to develop novel treatment strategies for SARS-CoV-2 and determine the effectiveness of antiviral, anti-inflammatory and immunomodulatory drugs, which are to be used with public health policy measures.[2]

Remdesivir, a nucleotide drug, has shown antiviral activity against beta coronaviruses, severe acute respiratory syndrome-associated coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus and SARS-CoV-2 by inhibiting viral RNA polymerase in vitro. The first experimental study was conducted in China. A randomized controlled trial (RCT) found that remdesivir contributed to good treatment outcomes for COVID-19 pneumonia.[3] A phase 3 RCT (the Adaptive COVID-19 Treatment Trial-1 [ACTT-1]) found that remdesivir reduced the median recovery time among patients with COVID-19 pneumonia requiring oxygen supplementation.[4]

Based on recent empirical studies, the effects of remdesivir on clinical improvement and mortality remained unclear. Evidence to show the effects of remdesivir on mortality in a subgroup of ventilation-treated patients was insufficient. Future studies should be conducted to provide more information on the efficacy and safety outcomes of remdesivir treatment, especially for different populations. This would allow us to draw more convincing conclusions about the potential benefits and harms of remdesivir.[5]
Favipiravir is used to treat COVID-19 globally. An open-label control study in China on the therapeutic effectiveness of favipiravir with lopinavir/ritonavir to treat COVID-19 showed a better therapeutic response for COVID-19 in terms of disease progression and viral clearance. However, some studies indicated that favipiravir did not correlate with clinical improvement or reduced mortality. In addition, data from large, prospective, blinded and placebo-controlled studies of favipiravir to treat severe COVID-19 still need to be included.[6] The authors investigated the potential benefits and harms of remdesivir compared with favipiravir treatment.
Currently, more data are needed concerning specific antiviral drugs to treat COVID-19. Several treatments are used.[7] Related studies have focused on clinical outcomes of remdesivir treatment with different results depending on the study design, i.e., time to start antiviral treatment and the severity of patients.[2, 8, 9] The present study was conducted to analyze the effects of remdesivir on clinical improvement, 14- and 28-day mortality and inhospital mortality of hospitalized patients with COVID-19 pneumonia at a local hospital in Thailand.

Methods

Study design

This study was approved by the Human Research Ethics Committee of Saraburi Hospital following international standards of human research ethics guidelines including the Declaration of Helsinki, the Belmont Report, the CIOMS Guideline, and the International Conference on Harmonization in Good Clinical Practice (Certificate No. EC036/2564).

This study comprised a nonrandomized therapeutic investigation using a retrospective observational cohort design including patients with COVID-19 pneumonia admitted to the modular ICU and the cohort ward at Saraburi Hospital, a provincial tertiary hospital, Thailand, between 1 June 2021 and 31 December 2021. Data were collected from Saraburi Hospital medical records such as demographic data, clinical data, severity scores, laboratory data and complications evaluating the therapeutic effects of remdesivir

(intervention group) and favipiravir (control group) along with standard care treatment. COVID-19 pneumonia was identified based on the International Classification of Diseases, Tenth Revision, and Clinical Modification codes (ICD-10) with diagnosis code J12.82.

The sample size was calculated based on samples of 30 patients with COVID-19 pneumonia in our pilot study, indicating that the proportion of clinical improvement was 0.63 in the remdesivir group and 0.48 in the favipiravir group. The authors determined the minimum sample size required to detect an absolute difference of 0.63 − 0.48 = 0.15 with 80% power using a two-sided test at $\alpha = 0.05$. A total sample of 344 individuals (172 individuals per group) was required to detect an absolute difference of 0.15 between the remdesivir and favipiravir groups. The sample size estimation was adequate based on the baseline adjustment using the propensity score method.

Inclusion criteria were as follows: (i) age ≥18 years; (ii) confirmed diagnosis of COVID-19 pneumonia (chest radiography [CXR] confirmed pneumonia and nasopharyngeal swab RT-PCR for COVID was positive); (iii) oxygen saturation (SpO2) ≤96%or a decrease in SpO2 of ≥3% from the initial measurement upon exercise (exercise-induced hypoxemia); (iv) a need for a low flow oxygen cannula (LFNC) of ≥5 L/min, for the use of a high flow nasal cannula (HFNC), or invasive mechanical ventilation (IMV) (WHO ordinary scale of clinical status = 4–6); (v) early phase of the disease (≤10 days from onset of symptoms) and (vi) alanine aminotransferase <5 times the upper limit of normal. Exclusion criteria were as follows: (i) patients with no need for oxygen supplementation (WHO ordinary scale of clinical status =1–3); (ii) patients using extracorporeal membrane oxygenation; (iii) patients lost to follow-up due to transfer to another hospital and (iv) patients with missing data such as COVID-19 vaccination history and laboratory results.

Clinical management

Remdesivir and favipiravir have been included in several local protocols worldwide. National clinical practice guidelines in Thailand recommend using favipiravir as the primary antiviral agent to treat COVID-19. Favipiravir is used alone among adults and children with a high risk of disease progression or with corticosteroids in cases of hypoxia or progressed pulmonary infiltrates. The favipiravir regimen suggested for adults is 2 × 1800 mg the first day and 2 × 800 mg daily days 2 to 5 or 2 to 10.

Patients with confirmed COVID-19 pneumonia became hypoxic (resting SpO2 ≤96%), showed a decrease in SpO2 of ≥3% upon exercise (exercise-induced hypoxemia) or had progression of pulmonary infiltration as shown by CXR. Therefore, depending on the clinical condition, Favipiravir 5 to 10 days is recommended. Patients should be closely monitored for symptoms. If not responding to treatment, a change to remdesivir may be considered in the following cases: (i) severe pneumonia less than ten days after symptom onset with an oxygen cannula of ≥5 L/min but with SpO2 <95% or when receiving HFNC/NIV or using an invasive mechanical ventilator, (ii) pregnancy with pneumonia or (iii) oral administration is contraindicated, or the patient has problems with absorption.

In addition, patients were provided anticoagulant therapy when they presented severe symptoms, no contraindications, no bleeding risk upon anticoagulant therapy and at least one of the following indications: d-dimer ≥6 times the upper normal limit, a history of venous thromboembolism or thrombophilia, active cancer, body mass index (BMI) ≥30 kg/m^2 and pregnancy.[10]

Data collection and measurements

The medical records of all enrolled patients were obtained from the digital database. Collected baseline prognostic factors included age, sex, BMI, symptoms, underlying disease, vital signs, SpO2, disease severity (pneumonia severity index [PSI/PORT score], quick sepsis-related organ failure assessment [qSOFA] and CURB-65), history of vaccination against

COVID-19, WHO ordinal scale[11] at baseline and 28 days after admission, length of hospital stay, CXR results (categorized in five groups: category 1=normal, no abnormality detected; category 5=multifocal, bilateral peripheral opacities or opacities with round morphology)[12] and laboratory results **(Table 1).**

The primary objective was to compare the effectiveness of remdesivir versus favipiravir in treating COVID-19 pneumonia. Clinical improvement was defined as patients being discharged alive and not having ≥2-point reduction in the WHO disease severity score during hospital treatment. The secondary objective was to compare 14-and 28-day mortality, in-hospital mortality, free from oxygen supplementation (without MV, HFNC and LFNC) and the WHO ordinary scale at day 28 between patients with COVID-19 pneumonia treated with remdesivir versus favipiravir. They were assessed using an ordinal eight-category WHO ordinary scale, where 1 to 2=ambulatory state, 3 to 4=hospitalized mild disease, 5 to 7=hospitalized severe disease and 8=dead.[11] Adverse events were also recorded.

Statistical analysis

Data were analyzed using Stata, Version 16.0 (StataCorp, Lakeway, TX, USA). A two-sided *p*-value of <0.05 was considered significant for all statistical analyses. For all clinical characteristics and relevant variables, descriptive statistics were calculated. Categorical data are presented as percentages, and continuous variables are presented as mean and standard deviation or median and interquartile range, as appropriate. Continuous variables were compared between the two groups with either the t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-square or Fisher's exact tests.

Statistical analyses were based on the objectives of the study using the propensity score method. The propensity score estimate was obtained from the multivariable logistic regression model: propensity matching scores were analyzed between the remdesivir and favipiravir groups at a 1:1 ratio. The covariate analyzed in the nearest neighbor propensity score matching model was selected based on risk factors affecting selection bias and a literature review, as well as some imbalanced covariates with significant differences between the two groups from the univariate analysis ($p<0.05$), i.e., age ≥60 years, sex, obesity (BMI ≥30 kg/m^2), diabetes, chronic kidney disease, cardiovascular disease, PSI/PORT score, CRP level,[13] and concomitant medication (tofacitinib), to reduce selection bias and confounding factors.[14]

Clinical improvement was compared, 14- and 28-day mortality, inhospital mortality, free from IMV, HFNC, LFNC and the WHO ordinary scale at day 28 between the two groups using multivariable Cox proportional hazard regression analysis and Kaplan–Meier estimator curves. Differences between the groups were shown using a stratified log-rank test. Complications and adverse events were also analyzed using a relative risk regression analysis reported as adjusted relative risk.

Results

Data were retrieved from 481 medical records from 1 June 2021 to 31 December 2021. Of these, 44 showed ineligible criteria: 25 had alanine aminotransferase >5 times the upper limit of normal, and 12 did not need oxygen supplementation. Four hundred thirty-seven patients with COVID-19 pneumonia met the inclusion criteria. Twenty-five were excluded because 13 had missing data, and 12 were referred to other hospitals. Four hundred twenty-five were included in this cohort; 244 were treated with remdesivir and 181 with favipiravir. **Table 1** shows demographic data, prognostic factors and confounding factors among 425 patients. After propensity score matching at a ratio of 1:1, 362 patients were enrolled and divided in the remdesivir and favipiravir groups (n=181 patients per group) **(Figure 1)**

Demographic characteristics and clinical symptoms of patients with COVID-19 pneumonia

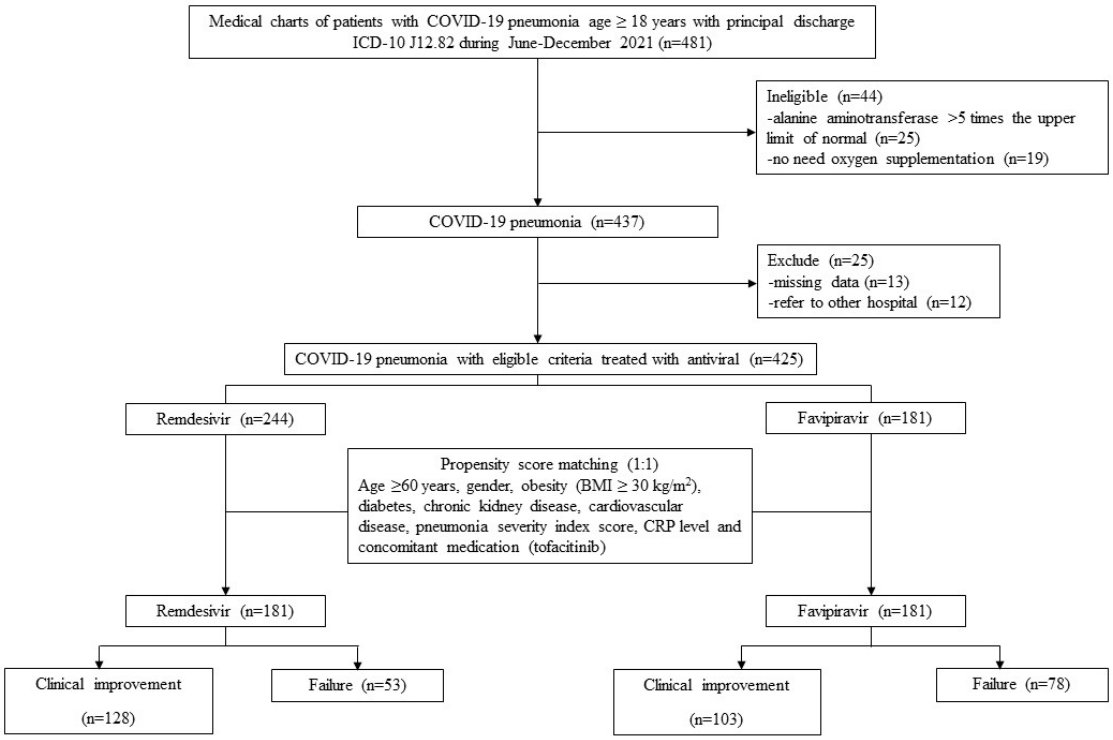


Figure 1. Study flow diagram of the patients' cohort

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
General characteristic						
Age, years	59.13±16.49	62.04±14.07	0.056	60.02± 17.29	62.04±14.07	0.223
Male, gender (%)	105(43.03)	81(44.75)	0.724	82(45.30)	81(44.75)	0.916
BMI, kg/m^2	29.46±7.57	28.57±6.54	0.205	28.86±7.39	28.57±6.54	0.688
Coexisting condition (%)						
Diabetes	121(49.59)	86(47.51)	0.672	91(50.28)	86(47.51)	0.599
Obesity	96(39.34)	65(35.91)	0.471	66(36.46)	65(35.91)	0.913
COPD	6(2.46)	3(1.66)	0.739	5(2.76)	3(1.66)	0.723
Cardiovascular disease	18(7.38)	20(11.05)	0.189	16(8.84)	20(11.05)	0.482
Cerebrovascular disease	21(8.61)	7(3.87)	0.051	13(7.18)	7(3.87)	0.167
Cirrhosis	3(1.23)	5(2.76)	0.294	2(1.10)	5(2.76)	0.449
Chronic kidney disease	21(8.61)	32(17.68)	0.005	21(11.60)	32(17.68)	0.137
Immunocompromise	0	2(1.10)	0.181	0	2(1.10)	0.499
Use steroid before	3(1.23)	0	0.265	3(1.66)	0	0.248
Hypertension	137(56.15)	111(61.33)	0.284	99(54.70)	111(61.33)	0.201

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group (Cont.)

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
Dyslipidemia	98(40.16)	54(29.83)	0.028	71(39.23)	54(29.83)	0.060
Alzheimer's disease	1(0.41)	0	1.000	1(0.55)	0	1.000
History of malignancy	3(1.23)	4(2.21)	0.466	3(1.66)	4(2.21)	1.000
Thalassemia	1(0.41)	1(0.55)	1.000	1(0.55)	1(0.55)	1.000
Autoimmune disease	3(1.23)	2(1.10)	1.000	3(1.66)	2(1.10)	1.000
HIV infection	1(0.41)	1(0.55)	1.000	1(0.55)	1(0.55)	1.000
Gout	16(6.56)	4(2.21)	0.039	15(8.29)	4(2.21)	0.010
Psychiatric disorder	2(0.82)	1(0.55)	1.000	2(1.10)	1(0.55)	1.000
Symptoms						
Fever	199(81.56)	135(74.59)	0.083	143(79.01)	135(74.59)	0.319
Cough	226(92.62)	165(91.16)	0.583	167(92.27)	165(91.16)	0.703
Diarrhea	25(10.25)	40(22.10)	0.001	19(10.50)	40(22.10)	0.003
Sore throat	24(9.84)	13(7.18)	0.337	16(8.84)	13(7.18)	0.561
Anosmia	20(8.20)	29(16.02)	0.012	11(6.08)	29(16.02)	0.003
Nausea	25(10.25)	19(10.50)	0.933	17(9.39)	19(10.50)	0.725
Vital sign						
Body temperature (°C)	37.89±4.05	37.51±1.09	0.213	38.04±4.66	37.51±1.09	0.135
RR(/min)	30.23±5.57	30.00±6.84	0.705	30.14±5.85	30.00±6.84	0.836
SpO2 room air (%)	85.31±7.35	86.72±7.39	0.052	85.87±7.17	86.72±7.39	0.270
Disease severity						
PSI	3.29±1.22	3.49±1.22	0.095	3.34±1.23	3.49±1.22	0.267
qSOFA	1.35±0.63	1.42±0.74	0.315	1.37±0.64	1.42±0.74	0.497
CURB 65	1.5(1,3)	2(1,3)	0.252	2(1,3)	2(1,3)	0.640
Baseline WHO ordinal scale of clinical status (%)						
4 = LFNC	28(11.48)	60(33.15)	<0.001	25(13.81)	60(33.15)	<0.001
5 = HFNC	191(78.28)	96(53.04)	<0.001	137(75.69)	96(53.04)	<0.001
6 = MV	26(10.66)	26(14.36)	0.249	20(11.05)	26(14.36)	0.430
Duration of oxygen support, days (IQR)	10(7,16)	10(7,18)	0.993	10(6,15)	10(7,18)	0.437
Hospital, days	13(10,18)	13(9,19)	0.707	12(9,17)	13(9,19)	0.485
Vaccine immunization (%)						
No vaccination	179(73.36)	152(83.98)		130(71.82)	152(83.98)	
CoronaVac	31(12.70)	14(7.73)		26(14.36)	14(7.73)	
CoronaVac / CoronaVac	5(2.05)	4(2.21)	0.111	5(2.76)	4(2.21)	0.063
AZ	20(8.20)	8(4.42)		15(8.29)	8(4.42)	
AZ/AZ	1(0.41)	1(0.55)		0(0)	1(0.55)	
CoronaVac /AZ	8(3.28)	2(1.10)		5(2.76)	2(1.10)	
Laboratory						
Routine peripheral blood						
WBC (x 10^3/μL) (IQR)	9.0 (6.45,11.25)	8.3 (5.70,12.20)	0.391	8.8 (6.10,10.90)	8.3 (5.70,12.20)	0.795
CBC neutrophil %	81.69±9.68	80.23±12.18	0.169	81.14±9.83	80.23±12.18	0.431
CBC Lymph % (IQR)	12 (7,19)	12 (7,19)	0.836	12(7,20)	12(7,19)	0.859

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group (Cont.)

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
ANC (x 10^3/μL) (IQR)	7.37 (4.78,9.73)	6.48 (4.22,10.21)	0.408	7.24 (4.49,9.43)	6.48 (4.22,10.21)	0.787
ALC (x 10^3/μL) (IQR)	0.98 (0.66,1.36)	935 (665,2380)	0.887	0.98 (0.60,1.38)	0.94 (0.67,2.38)	0.977
Hct (%)	37.43±6.51	36.73±6.49	0.274	36.91±6.92	36.73±6.49	0.800
Platelet (x 10^3/μL)	240±98	239±106	0.933	238±103	239±106	0.948
Blood biochemistry						
BUN (mg/dL) (IQR)	18.9 (12.6,28.35)	21.4 (13.7,37.6)	0.026	19.9 (13,31.3)	21.4 (13.7,37.6)	0.153
Cr (mg/dL) (IQR)	0.86 (0.65,1.18)	0.97 (0.69,1.42)	0.069	0.89 (0.68,1.27)	0.97 (0.69,1.42)	0.552
TB (mg/dL) (IQR)	0.60 (0.46,0.83)	0.63 (0.50,0.85)	0.145	0.61 (0.46,0.85)	0.63 (0.50,0.85)	0.277
DB (mg/dL) (IQR)	0.16 (0.10,0.25)	0.14 (0.10,0.27)	0.786	0.16 (0.10,0.26)	0.14 (0.10,0.27)	0.973
DB/TB ratio (IQR)	0.26 (0.21,0.32)	0.24 (0.20,0.31)	0.108	0.26 (0.21,0.32)	0.24 (0.20,0.31)	0.097
AST (U/L) (IQR)	51 (36,72)	48 (34,75)	0.721	47 (33,72)	48 (34,75)	0.822
ALT (U/L) (IQR)	38 (24.5, 59)	36 (33, 61)	0.648	35 (22,53)	36 (33,61)	0.149
Albumin (g/dL)	3.42±0.98	3.40±0.49	0.764	3.46±1.12	3.40±0.49	0.539
Blood sugar (mg/dL) (IQR)	172.5 (129,254)	171 (132,298)	0.325	171 (126,252)	171 (132,298)	0.162
Inflammatory marker						
CRP (mg/dL) (IQR)	98.2 (53.9,128.0)	76.9 (39.3,120.3)	0.010	91.2 (52.3,124.6)	76.9 (39.3, 120.3)	0.131
LDH (U/L) (IQR)	399.5 (325,588)	425 (309,559)	0.750	384 (298,561)	425 (309,559)	0.355
PT (sec) (IQR)	12.6 (11.8,13.55)	12.3 (11.7,13.2)	0.079	12.6 (11.8,13.6)	12.3 (11.7,13.2)	0.115
PTT (sec)	24.29±4.34	25.18±6.70	0.098	24.54±4.58	25.18±6.70	0.283
CT- value (N gene)	20.95±4.92	20.98±4.71	0.952	20.91±4.90	20.98±4.71	0.897
CXR category						
Category 1/2/3	9(3.69)	24(13.26)	<0.001	9(4.97)	24(13.26)	0.017
Category 4	27(11.07)	26(14.36)		23(12.71)	26(14.36)	
Category 5	208(85.25)	113(72.38)		149(82.32)	113(72.38)	
Onset of symptoms before antiviral initiation	6 (3.5, 8)	6 (2, 8)	0.256	6 (3, 8)	6 (2, 8)	0.155
Treatment						
Anti-inflammatory drugs						

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia by unmatched and propensity score-matched group (Cont.)

Characteristic	Unmatched cohort			Matched cohort		
	Remdesivir (n=244)	Favipiravir (n=181)	*p*-value	Remdesivir (n=181)	Favipiravir (n=181)	*p*-value
Dexamethasone	228(93.44)	172(95.03)	0.492	169(93.37)	172(95.03)	0.500
IVMP	20(8.20)	14(7.73)	0.862	17(9.39)	14(7.73)	0.573
Hydrocortisone	20(8.20)	8(4.42)	0.121	16(8.84)	8(4.42)	0.091
Tocilizumab	8(3.28)	5(2.76)	1.000	6(3.31)	5(2.76)	0.759
Tofacitinib	73(29.92)	8(4.42)	<0.001	10(5.52)	8(4.42)	0.629
Baricitinib	27(11.07)	4(2.21)	0.001	27(14.92)	4(2.21)	<0.001
Hemoperfusion	8(3.28)	1(0.55)	0.085	5(2.76)	1(0.55)	0.215
Hemodialysis	4(1.64)	1(0.55)	0.399	4(2.21)	1(0.55)	0.372
Mean propensity score	0.37±0.19	0.50±0.12	<0.001	0.49±0.06	0.51±0.07	0.010

IQR, Interquartile range; BMI, body mass index; RR, respiratory rate; PSI, pneumonia severity index; qSOFA, quick sepsis related organ failure; COPD, chronic obstructive pulmonary disease; LFNC, low flow nasal canular; HFNC, high flow nasal canular; AZ, AstraZeneca vaccine (ChAdOx1-S/nCoV-19 [recombinant] vaccine); ANC, Absolute neutrophil count; ALC, Absolute lymphocyte count; CXR, chest radiograph; IVMP, intravenous methylprednisolone

revealed 186 males (43.8%) and 239 females (56.2%), with a mean age of 61.0±15.8 years, a mean hospital duration of 14.7 ± 8.9 days, a median onset of symptoms before antiviral initiation of 6 days [IQR, 3–8] and a mean BMI of 28.7 ± 6.9 kg/m^2. Among co-existing conditions, hypertension was the most prevalent (248 patients, 58.4%), followed by diabetes (207 patients, 48.7%) and obesity (161 patients, 37.9%). The use of HFNC at baseline was higher in the remdesivir group than in the favipiravir group (78.3 vs. 53.0%; p <0.001), but the use of LFNC was lower in the remdesivir group than in the favipiravir group (11.5 vs. 33.2%; p<0.001). The use of tofacitinib (29.9 vs. 4.4%; p <0.001) and baricitinib (11.1 vs. 2.2%; p=0.001) was higher in the remdesivir group. The proportions of diarrhea (10.3 vs. 22.1%; p=0.001) and chest X-ray category 1 to 3 (3.7 vs. 13.3%; p<0.001) were lower in the remdesivir group than in the favipiravir group. No difference was noted in the duration of oxygen support, length of hospital stay, disease severity, vaccine immunization and the onset of symptoms before antiviral initiation between the two groups. The mean CRP level was significantly higher in the remdesivir group than in the favipiravir group (median, 98.2 [IQR, 53.9–128.0] vs. median, 76.9 [IQR, 39.3–120.3]; p=0.010) **(Table 1).**

The propensity scores were calculated with a multivariable logistic model using covariates comprising the abovementioned variables **(Table 2).** The mean propensity scores in each group significantly differed before matching (0.37 ± 0.19 vs. 0.50 ± 0.12; p<0.001) **(Table 1, Figure 2).** After 1:1 matching, 181 patients were allocated in each treatment group. This resulted in a decreased magnitude of the difference in mean propensity between the groups, but a significant difference remained between the groups (0.49 ± 0.06 vs. 0.51 ± 0.07; p=0.010). The propensity score model is shown in **Figure 3.** The propensity matching variables showed no statistically significant difference between the two groups: age (60.0 ± 17.3 vs. 62.0 ± 14.1; p=0.223), sex (male: 45.3 vs. 44.8%; p=0.916), obesity (BMI≥30 kg/m^2; 36.5% vs. 35.9%; p=0.913), diabetes (50.3 vs. 47.5%; p=0.599), chronic kidney disease (11.6 vs. 17.7%; p=0.137), cardiovascular disease (8.8 vs. 11.1%; p=0.482), pneumonia severity index score (PSI; 3.34±1.23 vs. 3.49±1.22; p=0.267), tofacitinib (5.5 vs. 4.4%; p=0.629) and CRP level (median,

Table 2. Derivation of propensity score equation from covariate by multivariate binary logistic regression

Covariates	Coefficient	95% confident interval	*p*-value
Age ≥60 years	-0.0954677	-0.569909,0.3789736	0.693
Male gender	0.0331352	-0.3907013,0.4569717	0.878
Obesity (BMI ≥30 kg/m^2)	-0.0204748	-0.464773,0.4238234	0.928
Diabetes	0.1698097	-0.2539996,0.593619	0.432
Chronic kidney disease	-0.587818	-1.26025,0.0846142	0.087
Cardiovascular disease	-0.079309	-0.8351409,0.6765229	0.837
PSI score	-0.1251413	-0.3355914,0.0853088	0.244
CRP level	0.0039724	0.0000179,0.0079269	0.049
Tofacitinib	2.177759	1.407167,2.94835	<0.001

PSI, pneumonia severity index; BMI, body mass index; CRP, c-reactive protein

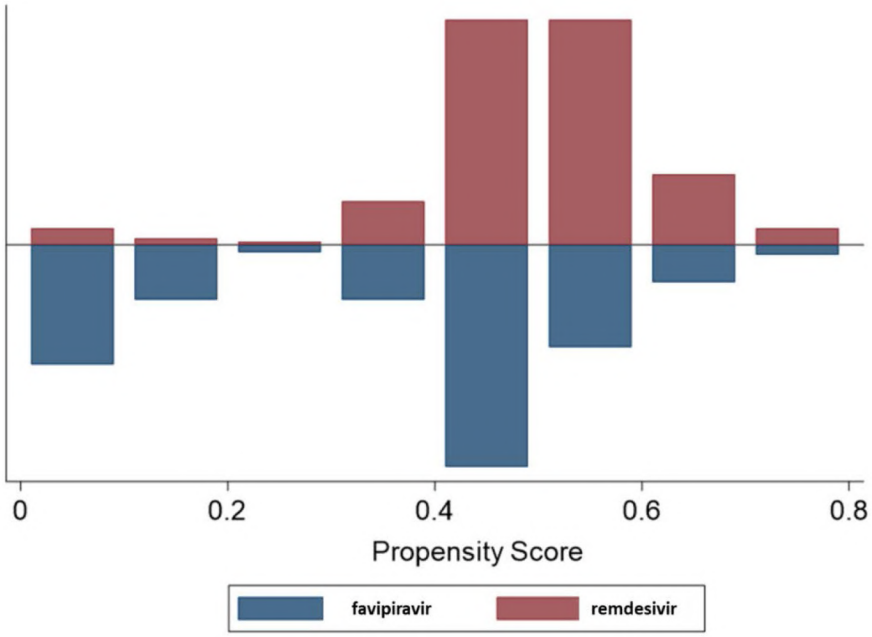


Figure 2. Mean propensity scores in each group

91.16[IQR,53.86–127.98]vs.median,76.92[IQR, 39.27–120.34]; *p*=0.131) **(Table 1).**

In addition, after matching, variables with an imbalance between groups ($p<0.05$) were CXR category 1 to 5 ($p=0.012$), HFNC (75.7 vs. 53.0%; $p<0.001$), LFNC (13.8 vs. 33.2; $p<0.001$), baricitinib (14.9 vs. 2.2%; $p<0.001$), gout (8.3 vs. 2.2%; $p=0.010$), diarrhea (10.5 vs. 22.1%; $p=0.003$), and anosmia (6.1 vs. 16.0%; $p=0.003$). Gout, diarrhea and anosmia were not associated with the outcomes[15], whereas CXR categories 1 to 5, HFNC, LFNC and baricitinib might be potential confounding factors influencing outcomes. Even though the authors tried to use propensity score matching with significant variables, an imbalance between groups was still found **(Table 1).**

Therefore, primary and secondary outcomes were analyzed by adjusting these variables in the final model with a multivariable Cox proportional hazard regression model **(Table 3)** and comparative analysis for complications and

adverse events in each group using multivariable logistic regression to adjust for residual confound bias **(Table 4).** As a result, remdesivir increased the proportion of clinical improvement by 52% (70.72 vs. 56.91%, adjusted HR=1.52 [1.16–2.01]; $p = 0.002$), reduced in-hospital mortality (adjusted HR=0.68 [0.47–0.99]; p=0.047) **(Table 3, Figures 4 A and 4D)**, increased the proportion of patients free from HFNC and LFNC use (74.34vs.56.10%, adjusted HR =1.79 [1.32–2.45]; p<0.001)(86.43 vs. 74.80%, adjusted HR=1.34 [1.01–1.78]; p=0.037) **(Figures 5B and 5C)**, and increased the median survival time (26 vs. 24 days, median survival time difference of 2 days [IQR, 2–6]; p=0.048). In addition, remdesivir significantly increased the proportion of WHO ordinary scale 1 to 2 (ambulatory with hospital discharge) (66.85vs.53.04%, adjusted HR=1.19 [1.01–1.41]; p=0.035) **(Table 3).**

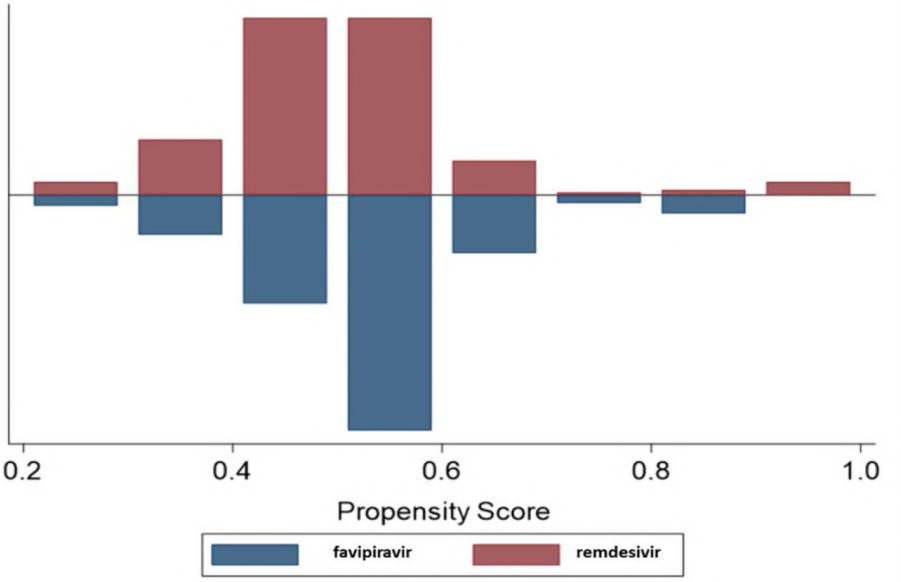


Figure 3. Distribution of the propensity scores between the two groups (remdesivir and favipiravir) among patients with COVID-19 pneumonia (after propensity score matching)

Table 3. Primary and secondary outcomes

Outcome	Treatment N (%)		Unadjusted analysis		Adjusted analysis	
	Remdesivir (n=181)	Favipiravir (n=181)	Crude HR 95%CI	*p*-value	Adjusted HR[a] 95%CI	*p*-value
Clinical improvement	128(70.72)	103(56.91)	1.39 (1.07,1.81)	0.013	1.52 (1.16,2.01)	0.002
Mortality						
14 days mortality	50(27.62)	76(41.99)	0.73 (0.51,1.04)	0.087	0.71 (0.49,1.04)	0.081
In-hospital mortality	50(27.62)	78(43.09)	0.70 (0.49,1.01)	0.053	0.68 (0.47,0.99)	0.047
28 days mortality	50(27.62)	78(43.09)	0.74 (0.52,1.05)	0.101	0.70 (0.48,1.02)	0.066
Median survival time,95%CI	26(21,33)	24(19,27)			2[b] (2-6)	0.048

Table 3. Primary and secondary outcomes (Cont.)

Outcome	Treatment N (%)		Unadjusted analysis		Adjusted analysis	
	Remdesivir (n=181)	Favipiravir (n=181)	Crude HR 95%CI	*p*-value	Adjusted HR[a] 95%CI	*p*-value
Free from oxygen supplementation						
Free from MV	8(22.22)	7(11.67)	1.22 (0.43,3.39)	0.702	1.17 (0.40,3.45)	0.765
Free from HFNC	113(74.34)	69(56.10)	1.81 (1.33,2.44)	<0.001	1.79 (1.32,2.45)	<0.001
Free from LFNC	121(86.43)	95(74.80)	1.35 (1.03,1.76)	0.029	1.34 (1.01,1.78)	0.037
WHO ordinary scale at day 28			OR(95%CI)		OR(95%CI)	
Ambulatory with hospital discharge at day 28 (WHO 1-2)	121(66.85)	96(53.04)	1.26 (1.06,1.49)	0.008	1.19 (1.01,1.41)	0.035
Hospitalized mild to severe disease (WHO 3-7)	11(6.08)	10(5.52)	1.1 (0.47,2.52)	0.822	1.44 (0.61,3.44)	0.405

HR, hazard ratio; OR, odds ratio; MV, invasive mechanical ventilator; HFNC, high flow nasal canular; LFNC, low flow nasal canular; WHO ordinary scale, World Health Organization Ordinal Scale; [a] multivariable analysis adjusted for potential confounders (CXR category, HFNC, LFNC and baricitinib); [b] median survival time difference

Regarding complication events throughout the study period, 128 (70.72%) occurred in the remdesivir group and 103 (56.91%) in the favipiravir group. Remdesivir was associated with a significantly red0uced risk of acute respiratory failure (COVID-19 pneumonia progression) (29.8 vs. 34.8%, adjusted RR=0.96 [0.96–0.97]; $p<0.001$). In addition, remdesivir reduced the risk of shock and transaminitis more than favipiravir (18.8 vs. 28.2%, adjusted RR=0.66 [0.47–0.91]; $p=0.014$) (10.5 vs. 20.4%, adjusted RR=0.51 [0.30–0.88]; $p=0.015$) **(Table 4).**

Table 4. Comparison of complications and adverse events among patients with COVID-19 pneumonia in each group

Complication event	Remdesivir (n=181)	Favipiravir (n=181)	Adjusted RR[a] (95% CI)	*p*-value
Acute respiratory failure	54(29.83)	63(34.81)	0.96(0.96, 0.97)	<0.001
Secondary bacterial infection	38(20.99)	37(20.44)	1.26(0.87, 1.79)	0.212
Coinfection organism				
Acinetobacter baumannii	20(11.05)	16(8.84)	1.59(0.88,2.89)	0.123
Pseudomonas aeruginosa	6(3.31)	12(6.63)	0.47(0.16,1.35)	0.164
Klebsiella pneumoniae	15(8.29)	8(4.42)	2.23(0.95,5.22)	0.063
Candida spp.	16(8.84)	13(7.18)	1.07(0.50,2.31)	0.848
Escherichia coli	13(7.18)	7(3.87)	1.77(0.69,4.51)	0.227
Staphylococcus aureus	1(0.55)	3(1.66)	0.34(0.03,3.35)	0.358

Table 4. Comparison of complications and adverse events among patients with COVID-19 pneumonia in each group (Cont.)

Complication event	Remdesivir (n=181)	Favipiravir (n=181)	Adjusted RR[a] (95% CI)	*p*-value
Aspergillus spp.	6(3.31)	3(1.66)	1.58(0.36, 6.89)	0.538
Enterococcus cloacae	3(1.66)	2(1.10)	1.68(0.27,10.30)	0.571
Stenotrophomonas spp.	2(1.10)	1(0.55)	1.85(0.16, 20.78)	0.615
Urinary tract infection	14(7.73)	11(6.08)	1.25(0.56, 2.78)	0.572
Acute kidney injury	42(23.20)	45(24.86)	0.97(0.67, 1.40)	0.891
Shock	34(18.78)	51(28.18)	0.66(0.47, 0.91)	0.014
DIC	2(1.10)	4(2.21)	0.64(0.11,3.50)	0.611
Metabolic acidosis	15(8.29)	22(12.15)	0.67(0.36, 1.25)	0.217
Pneumothorax	5(2.76)	3(1.66)	1.79(0.40,7.93)	0.439
UGIH	7(3.87)	6(3.31)	1.44(0.47, 4.33)	0.515
Transaminitis	19(10.50)	37(20.44)	0.51(0.30,0.88)	0.015
Alcohol withdrawal syndrome	1(0.55)	4(2.21)	0.22(0.02,1.96)	0.176
DKA	4(2.21)	7(3.87)	0.69(0.20,2.39)	0.569
CRBSI	7(3.87)	1(0.55)	7.31(0.89,59.78)	0.063
AF with RVR	4(2.21)	4(4.42)	0.54(0.16,1.79)	0.319

RR, relative risk; DIC, disseminated intravascular coagulation; UGIH, upper gastrointestinal hemorrhage; DKA, diabetic ketoacidosis; CRBSI, catheter-related blood stream infection; AF with RVR, atrial fibrillation with rapid ventricular response. [a] multivariable analysis adjusted for potential confounders (CXR category, HFNC, LFNC and baricitinib)

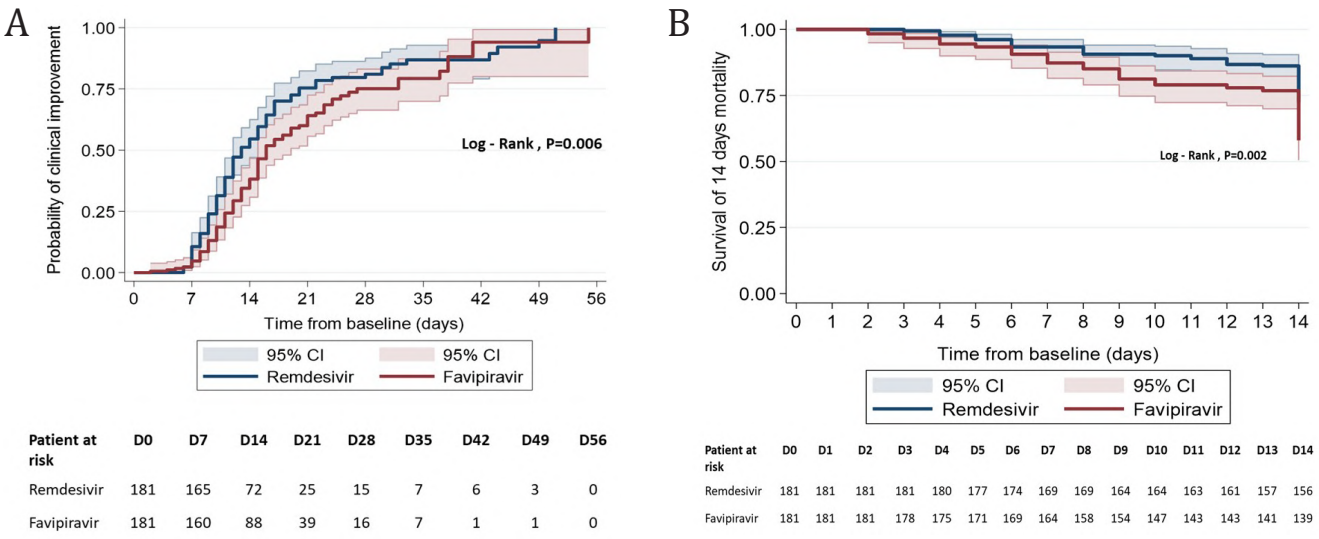
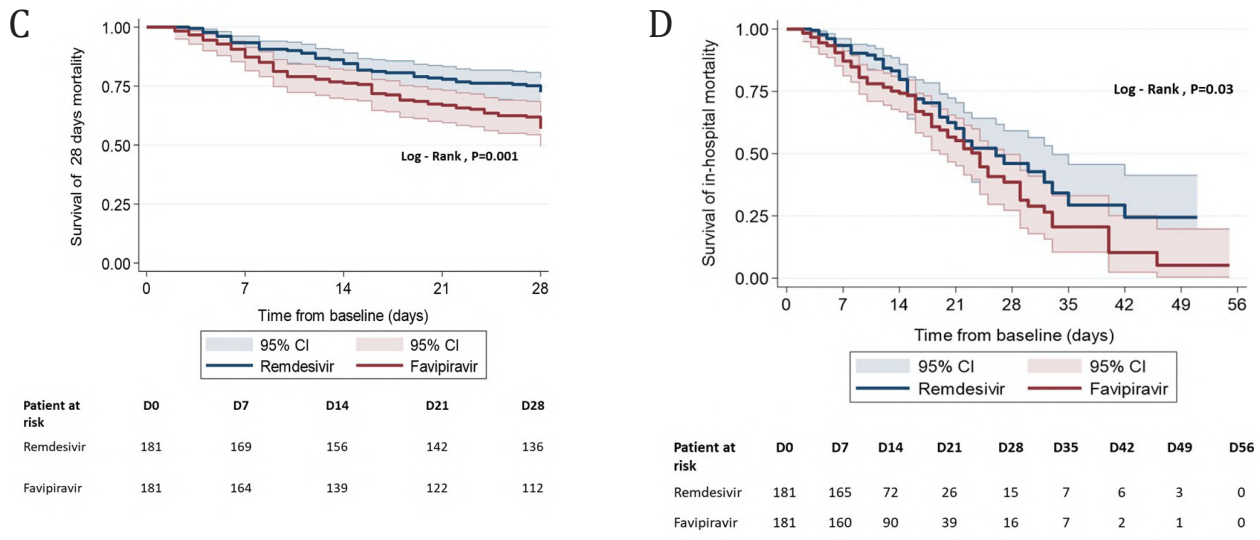


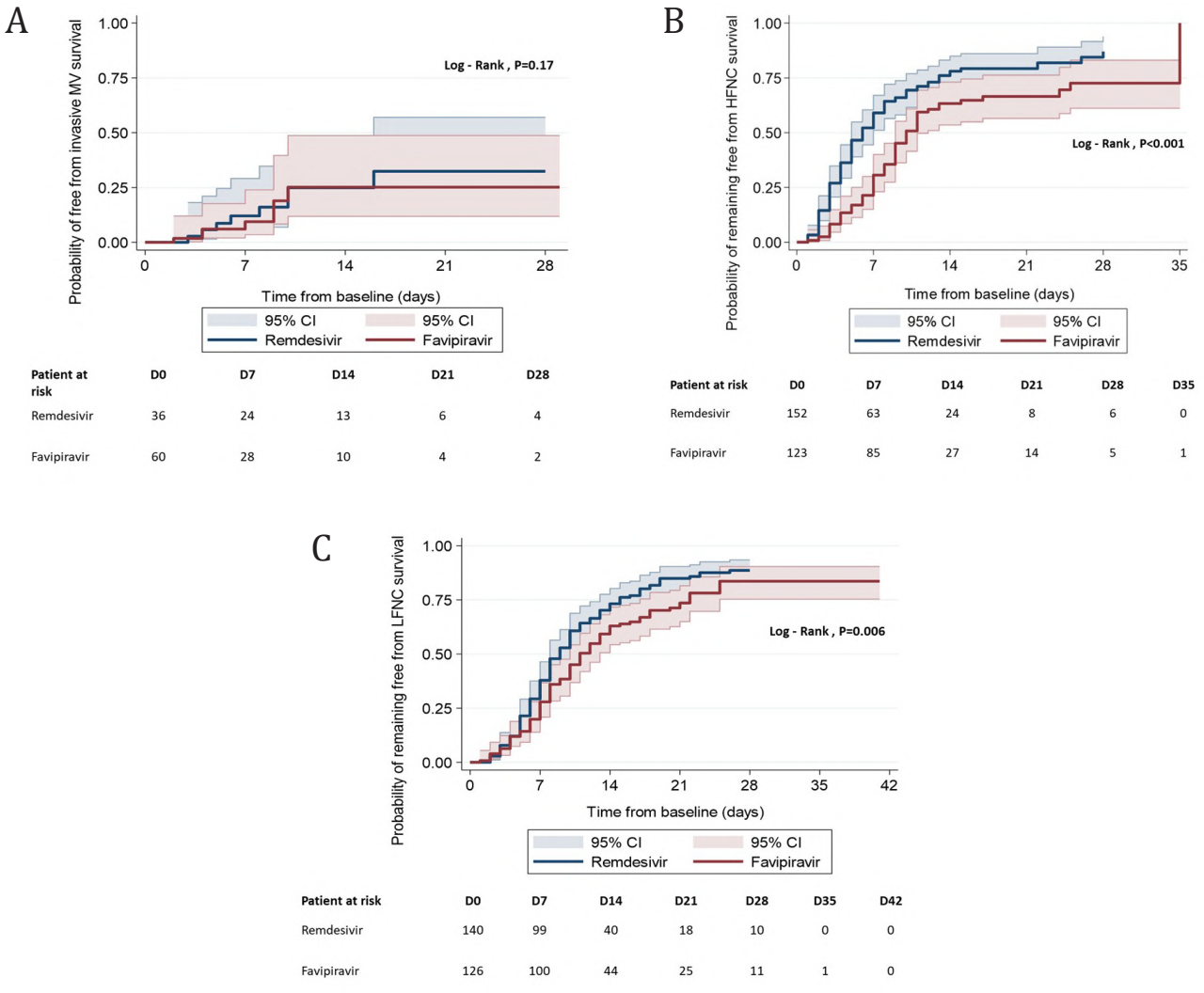
Figure 4. Survival plots of clinical improvement (A), 14-day mortality (B), 28-day mortality (C) and in-hospital mortality (D) from cause specific hazard analysis between the remdesivir and favipiravir treatment groups



Patient at risk	D0	D7	D14	D21	D28
Remdesivir	181	169	156	142	136
Favipiravir	181	164	139	122	112

Patient at risk	D0	D7	D14	D21	D28	D35	D42	D49	D56
Remdesivir	181	165	72	26	15	7	6	3	0
Favipiravir	181	160	90	39	16	7	2	1	0

Figure 4. Survival plots of clinical improvement (A), 14-day mortality (B), 28-day mortality (C) and in-hospital mortality (D) from cause specific hazard analysis between the remdesivir and favipiravir treatment groups (Cont.)



Patient at risk	D0	D7	D14	D21	D28
Remdesivir	36	24	13	6	4
Favipiravir	60	28	10	4	2

Patient at risk	D0	D7	D14	D21	D28	D35
Remdesivir	152	63	24	8	6	0
Favipiravir	123	85	27	14	5	1

Patient at risk	D0	D7	D14	D21	D28	D35	D42
Remdesivir	140	99	40	18	10	0	0
Favipiravir	126	100	44	25	11	1	0

Figure 5. Kaplan-Meier curves for the probability of remaining free from invasive mechanical ventilation (A), HFNC (B), and LFNC (C). Remaining free from oxygen supplementation was evaluated by cause specific hazard analysis between remdesivir and favipiravir treatment groups

Discussion

The first double-blind, randomized, placebo-controlled trial to study the efficacy of remdesivir among adults was the ACTT-1. Results showed that remdesivir was superior to placebo in terms of shortening the time to recovery among hospitalized patients with COVID-19 pneumonia (rate ratio for recovery, 1.29; 95%CI, 1.12–1.49; $p<0.001$, log-rank test).[16]

This presented study showed that remdesivir significantly increased the proportion of clinical improvement and reduced in-hospital mortality. The results of this study were consistent in clinical improvement and mortality benefit, with several related studies examining the efficacy of remdesivir.[16, 19, 20] Remdesivir treatment in the early stages of COVID-19 is important, as remdesivir phase 3 trials showed that both 10-and 5-day remdesivir treatment improved the time to recovery for hospitalized patients with COVID-19 pneumonia.[17] In a subsequent RCT, remdesivir, administered within seven days after the onset of COVID-19, among patients with high risk COVID-19 progression (age ≥60 years, hypertension, cardiovascular disease, cerebrovascular disease, diabetes, immuno-compromised, mild to moderate chronic kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease) reduced the risk of hospitalization and death.[18] Although remdesivir was the standard treatment for patients with COVID-19 pneumonia requiring oxygen supplementation, the benefits of remdesivir treatment remained unclear. In the present study, the authors compared the efficacy of remdesivir vs. favipiravir, in which both groups received standard care, corticosteroid and anticoagulant treatment, as indicated. During this study, 57% (244/425) of patients received remdesivir, and 43% (181/425) received favipiravir at the modular ICU and cohort ward. The results of this study agreed with a retrospective comparative study by Garibaldi et al.[19] reporting that remdesivir was associated with faster clinical improvement. This was consistent with a related study. The results of the ACTT-1 study suggest that remdesivir could shorten recovery time among patients with COVID-19 and lower respiratory tract infections requiring oxygen supplementation. In addition, patients receiving LFNC had the greatest benefit from remdesivir.[16] This was similar to our findings in that remdesivir significantly increased the proportion of cases free from HFNC and LFNC, while all patients in our cohort had COVID-19 pneumonia requiring oxygen supplementation at baseline. This current study showed similar clinical improvement benefits to those mentioned studies, especially among patients requiring oxygen supplementation. In conclusion, remdesivir might enhance clinical improvement and significantly increase the proportion of cases free from HFNC and LFNC use.

This might be explained by the fact that each antiviral drug has a different antiviral effect. Almoosa et al.[6] reported that favipiravir was not associated with significantly improved clinical symptoms among patients with severe COVID-19 pneumonia. They also found that patients receiving favipiravir presented a longer duration of fever and were more likely to require IMV and experience ARDS progression compared with the control group. Favipiravir may produce a weak antiviral effect in treating patients with severe COVID-19. Although no significant reduction was noted in 14- and 28-day mortality among patients receiving both remdesivir and corticosteroids, possibly due to the small sample size, this combination tended to reduce deaths. In the present study, remdesivir was significantly associated with a reduction of 32% in in-hospital mortality compared with favipiravir. Our findings were consistent with a study conducted in Denmark[20] and the ACTT-1,[16] reported that remdesivir could reduce 30-day mortality. An open-label, randomized clinical trial in Malaysia[21], conducted to study the efficacy of favipiravir compared with standard care, revealed that early treatment with oral favipiravir did not prevent their disease progression from nonhypoxia to hypoxia, nor did it significantly reduce in-hospital mortality among patients with COVID-19 at high risk of

disease progression (2.0 vs. 0%; OR=2.54; 95% CI: 0.76–207.84; *p*=0.08).

In the present study, favipiravir exhibited fewer effects on clinical improvement and mortality than remdesivir. A systematic review and meta-analysis by Hassanipour et al.[22] revealed that favipiravir might not reduce mortality among patients with COVID-19 with mild to moderate symptoms. In vitro studies have shown that remdesivir was highly effective in inhibiting pathogenic human coronaviruses, including SARS-CoV, Middle Eastern respiratory syndrome coronavirus, SARS-CoV-2 and Ebola virus.[23]

Additionally, in animal studies, Szemiel et al.[24] reported the effects of high dose favipiravir for treating SARS-CoV-2-positive hamsters. The drug had an antiviral effect but was not found to improve recovery rates. Simultaneously, remdesivir was studied in monkeys with SARS-CoV-2. Remdesivir reduced pulmonary infiltration on CXR and virus titer in bronchoalveolar lavages after 12 hours of treatment, although viral shedding from the upper respiratory tract did not decrease. This suggested that remdesivir possessed a potential anti-SARS-CoV-2 activity that may be more pronounced in the early treatment of infection.[25] No evidence of benefit exists comparing efficacy between remdesivir and favipiravir. Therefore, based on our results, remdesivir may be a promising drug for treating COVID-19 pneumonia requiring oxygen supplementation.

An inconsistency with the WHO Solidarity Trial was noted, which reported that remdesivir, hydroxychloroquine, lopinavir and interferon regimens had little effect on reducing overall mortality, IMV and length of hospital stay.[26] Subsequently, one trial reported that remdesivir had no clinical benefit among patients with COVID-19 pneumonia requiring oxygen supplementation. Moreover, in a double-blind, placebo-controlled, multicenter trial in China, remdesivir showed no difference in time to clinical improvement (HR =1.23 [95% CI 0.87–1.75]) compared with controls.[8] Most patients in this study (approximately 80%) were treated with corticosteroid 65 to 70 %, presenting mild symptoms and requiring LFNC. The remaining 10 to 20% were patients requiring HFNC or NIV. In two studies, a conflict was observed with our findings concerning clinical improvement. This might have stemmed from patients in the WHO solidarity cohort presenting less severe symptoms and a smaller proportion of HFNC use, so no significant difference was found in the clinical benefit of remdesivir. However, in our study, the majority of cohort patients had HFNC use 60 to 70% and LFNC use 30 to 40%, showing greater symptom severity than that of the WHO solidarity trial. This might explain the significant clinical benefit of remdesivir in a recent study.

Regarding complications, the present study indicated that remdesivir reduced the risk of acute respiratory failure (COVID-19 pneumonia progression). This was consistent with a prospective, observational study by Falcone et al.,[27] reporting that remdesivir could reduce the risk of progression to severe disease among up to 55% of hospitalized patients with COVID-19 pneumonia within five days of symptom onset. Another RCT, which included 562 nonhospitalized patients with a high risk of COVID-19 progression treated with remdesivir for three days, showed that remdesivir could reduce the risk of hospitalization and death by 87% compared with placebo.[18]

In this study, the proportion of transaminitis was smaller in the remdesivir group compared with the favipiravir group. The mechanism of drug-induced liver injury might be the idiosyncratic reaction of favipiravir or its derivatives. This remains unknown as favipiravir is metabolized via the liver by aldehyde oxidase and xanthine oxidase.[28] Kaur et al.[29] reported common side effects of favipiravir are increases in hepatic enzyme levels (23.7%), QT prolongation (5.4%) and skin and subcutaneous tissue disorders (15.4%). On the other hand, remdesivir has also been reported to be involved in drug-induced liver injury. It may have resulted from a reaction between P-glycoprotein (P-gp) inhibitors and remdesivir, where P-gp inhibitors result in decreased excretion of remdesivir from hepatocytes, leading to increased hepatocyte concentrations beyond the toxic threshold and

direct hepatotoxic effects. Elevations of AST and ALT levels were associated with the use of remdesivir for treating COVID-19, which were generally mild to moderate in severity and symptoms and often resolved on their own without jaundice; therefore, the liver enzyme should be monitored periodically during treatment.[30]

The strength of this study was that the treatments were based in routine clinical practice, consistent with the context of the local practice guidelines in Thailand. During treatment, side effects and complication events were monitored. Moreover, double adjustment was used to remove residual confounding factors. After propensity score matching, we also found an imbalance of the variables in both groups. Therefore, using multivariable regression adjustment could dramatically remove residual confounding bias.[14]

However, this study encountered several limitations. Firstly, it employed a retrospective observational cohort design; residual and unmeasured confounders could not be controlled, which might have interfered with evaluating treatment outcomes. Secondly, the sample size was small. Especially the results should be confirmed through analyses with propensity scores matching larger sample sizes. This should be tested in an RCT. Thirdly, the mean propensity score in both groups remained significantly different. The authors attempted to adjust the propensity score in the final model to reduce residual confounders. However, the results did not change the direction of treatment outcomes. Finally, the time from symptom onset to the start of antiviral treatment might have affected the outcomes. The authors could not adjust this variable for analyzing the outcomes because insufficient data records were in the digital database.

In the future, more RCTs should be conducted to determine the effectiveness of remdesivir among patients with COVID-19 pneumonia, including sufficient sample size. This will help to confirm our findings and better understand the efficacy of remdesivir treatment. In addition, further studies on the effectiveness of remdesivir at higher doses and coadministration with other antiviral drugs (SARS-CoV-2 neutralizing antibodies) and IL-1, IL-6, or TNF-α inhibitors to reduce immunopathological host responses affecting the severity of COVID-19 should be conducted in the future.

Conclusion

In summary, the present study provides evidence that patients with COVID-19 pneumonia requiring oxygen supplementation should be treated with remdesivir to increase clinical improvement, reduce in-hospital mortality and increase cases free from HFNC and LFNC use. However, this should only occur when compared to favipiravir treatment in a specific population.
Availability of data and materials

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Competing interests

The authors declare they have no conflicts of interest directly relevant to the content of this article.

Availability of data and materials

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

Author contributions

All authors have made substantial contributions to this work and have approved the final version of the manuscript. Concept and design: SK and WN. Acquisition of data: SK. Statistical analysis: PTd. Interpretation of data: SK, WN, and PTd. Writing original draft: SK, PTc, and WN. Writing review and editing: all authors.

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COST-UTILITY OF VARIOUS BIOLOGIC VERSUS ENDOPROSTHETIC RECONSTRUCTION FOR PRIMARY BONE SARCOMA OF THE HUMERUS

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Abstract

Background: The development of bone sarcoma treatment has resulted in a higher survival rate of patients including the developed surgical treatment called limb salvage surgery. Reconstructive surgery plays a vital role among patients and their quality of life after treatment. However, cost-effectiveness is another crucial factor in choosing a treatment method.

Methods: Eighteen patients with osteosarcoma were recruited in this study. All were treated using limb salvage surgery. The data were collected using the utility coefficient from the EQ-5D-5L Health Questionnaire. The patient's medical cost was obtained from Phramongkutklao Hospital, and all data were calculated for cost-effectiveness using the cost-utility analysis.

Results: Endoprosthesis reconstruction exhibited the highest utility value of 0.85 QALY and the lowest treatment complications. Nevertheless, the most increased cost was an average of 238,432.34 THB. In terms of cost, the recycled autograft showed the lowest treatment cost at an average of 60,774.61 THB. However, the complication of this method was quite severe, with a 50% recurrence rate. Allograft reconstruction was the most cost-effective method with a lower cost than endoprosthesis reconstruction (61,341.40 THB), despite having a lower utility of 0.49 QALY.

Conclusion: This study reported that endoprosthesis reconstruction resulted in more optimistic patient well-being but still indicated high cost. Using one-way sensitivity analysis, the QALY gain was only 16.9% of Thai per capita. When the cost of endoprosthesis reconstruction was reduced by only 15%, it could replace allograft reconstruction. In addition, an increase of the QALY, gaining only 20% of the average Thai per capita, would be cost-effective when the expense of endoprosthesis reconstruction was reduced by 4%.

Keywords: Primary bone sarcoma, Humerus bone cancer, Bone reconstruction, Cost-utility analysis, Various biologic reconstruction, Endoprosthesis reconstruction

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Introduction

Bone sarcoma, a tumor that forms in bone tissue, is most often diagnosed among people under age 35.[1] Tumors are found on the limbs more than in other regions.[1] This defect affected the patient's quality of life. The development of cancer treatment has improved the survival rate of patients[2]; moreover, limb-salvage surgery was developed helping to preserve the patient's limbs.[3, 4] This study discussed bone replacement surgery after tumor removal. The study aimed to compare the cost-effectiveness in terms of cost-utility, namely, the health economy process, to use as treatment decision-making information to enhance the best benefit for the patient's future quality of life of bone cancer.

From the relevant literature review search involving PubMed and Google Scholar, using the keywords "Musculoskeletal sarcoma and functional outcome and Evaluation and Health-related quality of life and cost-effectiveness and cost-utility," no study was found concerning assessing cost-utility analysis regarding bone cancer treatment in Thailand. However, only one study by Wilson et al. described the comparison of reconstruction surgery in primary bone sarcoma of the knee.[4] Additionally, Sande et al. only focused on the results of various surgery techniques without comparing their effectiveness. [5] It reported the metallic replacement method for patients with bone sarcoma, receiving reconstruction of the proximal humerus after cancer excision, showing a lower side-effect rate than using bone from donors. Moreover, the metallic replacement method established a significantly higher implant survival rate and better functional results than using donated bone. Nonetheless, patients still needed help with the metallic replacement method because the cost was high. The study aimed to assess the cost-utility of reconstructive surgical procedures with various biological reconstruction techniques, i.e., osteoarticular allograft and recycled bone autograft, compared with endoprosthetic reconstruction among patients with primary bone sarcoma of the humerus.

Methods

This research constituted a retrospective analysis study targeting patients with primary bone sarcoma of the humerus undergoing limb-sparing surgery at the Department of Orthopedics, Phramongkutklao Hospital, from 2012 to 2022. The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department, IRBRTA 1386/2565. The study included all patients receiving a diagnosis of primary bone sarcoma of the humerus and those undergoing limb-sparing surgery. Patients having a distant metastasis or recurrent lesion area were excluded when assessed using the EQ-5D-5L Health Questionnaire. Those who could not be assessed using the EQ-5D-5L Health Questionnaire or did not voluntarily provide additional information in the case of incomplete information in the PMK Musculoskeletal Oncology Patient Database (PMK-MOPD) were also excluded. In total, 18 patients met the requirements.

Permission to access expenses information was requested including medical costs from medical records, hospital patient billing data and funds that the National Health Security Office (NHSO) reimbursed to the hospital according to the Joint Disease Diagnosis Group (DRG) charges from the director of Phramongkutklao Hospital.

EQ-5D-5L Health Questionnaires were used to collect assessment information from the database PMK-MOPD. When any incomplete form was found, the researcher contacted the patient for more details with an understanding of informed consent.

Cost-utility of medical treatment was calculated using the currency in THB per quality adjusted life-year (QALY) accessed by life year-gained (LYG) with utility from EQ-5D-5L Health Questionnaire assessment and literature review.

Outcome Measurement

The QALY was obtained using the utility coefficient from the EQ-5D-5L Health Questionnaire. The QALY revealed the database displaying the health status of each surgery method in Thailand, leading to cost-utility analysis comparing the cost-effectiveness of different surgical procedures with direct medical costs.

Data Collection

Demographic data: The demographic data were collected from the patient's database at the Musculoskeletal Oncology Unit, Department of Orthopedics, Phramongkutklao Hospital; PMK Musculoskeletal Oncology Patient Data (PMK-MOPD), consisting of the physical and clinical data of participants.

Cost: In this study, we focused only on direct medical costs, comprising the patient hospital charges and the National Health Security Office (NHSO) reimbursements to the hospital according to the Diagnosis-Related Group (DRG charge). The reasons for using those costs were that they represented the same standard in all areas without confounding factors (such as economic status, travel expense and living expense), and could be measured. All patients assumed direct nonhealth care and indirect costs equally. The direct nonhealth care costs consisted of travel, accommodation, meals and the time value of informal care lost. The indirect costs comprised the cost of sick leave because the patient might have been unable to remain active and maintain a daily life on a sick day.

Utilities: The utility data were obtained from the patient's database at the Musculoskeletal Oncology Unit, Department of Orthopedics, Phramongkutklao Hospital; PMK Musculoskeletal Oncology Patient Data (PMK-MOPD) and were collected using the EQ-5D-5L Health Questionnaire assessment format. Grobet et al. showed that the utility value of the metallic replacement method was 0.85 and reduced by 25% per the QALY when the revision surgery was performed. [6] Losina et al.[7] and Gundle et al.[8] demonstrated that the utility value among patients requiring limb amputation after conservative treatment was 0.48 per the QALY (0.48). Wilson et al. revealed that the utility values among patients with non-operative complications such as infection were reduced by 12.5%. [9]

Data analysis

Health value or the QALY, which was obtained from the EQ-5D-5L questionnaire, was acquired in the utility value when multiplied by the number of LYG, in which the general cancer treatment standard was used, and the cancer was considered cured after ten years of follow-up without noting a recurrence of the disease. Here, the indication of cost-effectiveness in a QALY was represented by a COST/QALY value, also known as the cost-utility, which was obtained by quantifying the cost of each treatment option per QALY. Moreover, this study also revealed the surgery method showing the most cost-effectiveness when comparing the QALY gain ratio, i.e., the ratio between the cost and healthy years of the two surgeries compared.

Finally, the cost-effectiveness could be forecasted when the cost of each method was reduced to an acceptable value. This result was called one-way sensitivity analysis, which showed a cost-effectiveness acceptability curve. The curve represented the relationship between the willingness to pay per QALY (x-axis) and the probability that the choice would be worthwhile (y-axis).

Results

The patient database showed 32 patients meeting the study inclusion criteria. The patients were divided in two groups: 30 receiving bone tumor resection and reconstruction and two needing amputation because cancer had spread too much in nearby areas. However, 12 of all patients were excluded due to: 1) the spread of a tumor or cancer to distant parts of the body from its original site (n=8), 2) the postoperative recurrence of the tumor at the original site before completing the EQ-5D-5L questionnaire (n=1) and 3) the incomplete response of the EQ-5D-5L questionnaire (n=3).

The mean age of the included patients was 24.56 years, ranging from 9 to 45 years. Since patients received their first treatment, the follow-up time was 331 to 1,567 days (an average of 889 days). The male ratio was relatively higher than that of females (male-to-female ratio = 10:8). Only the two most common types of diagnosed cancers were included, namely, osteosarcoma (n=12) and Ewing sarcoma (n=6), occurring more often right- than left-sided **(Table 1).**

Table 1. Patient characteristics

Data	Content	Number (Total 18)	%
Gender	Male	10	55.56
	Female	8	44.44
Diagnosis	Osteosarcoma	12	66.67
	Ewing sarcoma	6	33.33
Side	Right	10	55.56
	Left	8	44.44

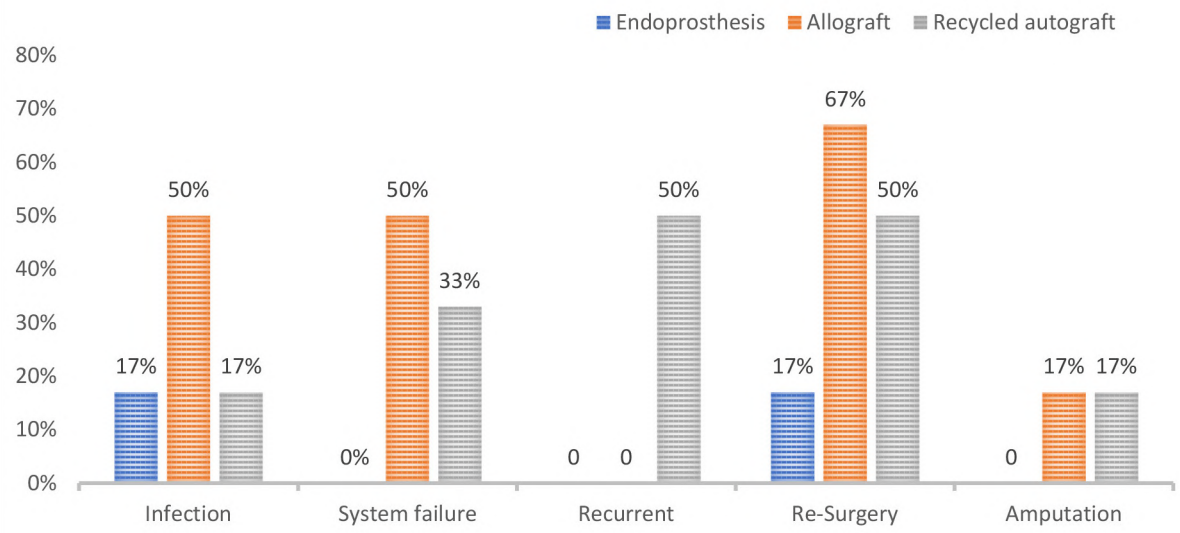

Figure 1. Complications of reconstruction methods

Regarding the incidence of complications, patients with metallic endoprosthetic reconstruction had the lowest rate of developed complications, comprising only one case. However, the revision surgery was completed, while other reconstructive surgery methods presented more complications. Six patients showed complications with allograft reconstruction, divided into three patients with infection and three patients with systemic failure, of whom four patients underwent revision surgery, and one had an arm amputated because of uncontrollable complications. Three patients presented complications in recycled autograft surgery, divided in one patient with infection and two patients with systemic failure. However, this was the only treatment that presented three cases of recurrence. All patients had undergone revision surgery. Those complications directly affected the utility value among three patients, one needing amputation, as shown in **Figure 1.**

This study obtained the utility value from the patient's database at the Musculoskeletal Oncology Unit, Department of Orthopedics, Phramongkutklao Hospital; PMK Musculoskeletal Oncology Patient Data (PMK-MOPD). The EQ-5D-5L Health Questionnaire assessment format was used to determine the utility value (Utility, U) according to the Health Technology Assessment Handbook for Thailand. (10) The literature review indicated that the utility value of metallic endoprosthesis reconstruction was the highest [6] compared with allograft and recycled autograft reconstruction (0.85QALY, 0.49QALY and 0.41QALY, consecutively) **(Table 2)**

This current study found that the average cost of endoprosthesis reconstruction was higher than other biologic reconstructions, having equivalent values (238,432.34 THB and 61,502.57 THB, respectively). The comparison of QALY showed that the allograft reconstruction was the most promising cost-effective method; however, focusing

Table 2. Utility of patients, based on reconstruction methods and complications.

Parameter	Utility	References
Reconstruction Methods		
Endoprosthetic Reconstruction	0.85 QALY	Grobet CE et al.[7]
Osteoarticular Allograft	0.49 QALY	PMK-MOPD
Recycled Bone Autograft	0.41 QALY	PMK-MOPD
Biologic Reconstruction (Allograft & Recycled Bone Autograft)	0.44 QALY	PMK-MOPD
Each Re-Surgery	↓25%	Losina E et al.[8]
Amputation	0.4800 QALY	Gundle KR et al.[9]
Non-Operative complications	↓12.5%	Wilson RJ et al.[5]

Table 3. Cost-utility analysis of reconstruction methods compared with endoprosthesis

Reconstruction Methods	Cost	QALY	Cost/QALY	QALY gain (Compare with Endoprosthesis)
Endoprosthesis	238,432.34 (180,653.76 – 300,323.55)	8.5	28,050.86	
Allograft	61,341.40 (31,152.98 – 109,132.44)	4.9	12,518.65	49,191.93
Recycled Bone Autograft	60,774.61 (21,017.71 – 98,115.03)	4.1	14,823.08	40,376.76
Biologic (Allograft & Autograft)	61,502.57 (21,017.71 – 109,132.44)	4.4	13,977.86	43,153.60

on only the health outcome displayed that the high utility treatment constituted a healthy person treated with endoprosthesis reconstruction. Therefore, further comparing the cost-effectiveness of different reconstructive surgery methods was needed individually. Those results are exhibited as the QALY gain in **Table 3.** Data were also analyzed using a one-way sensitivity method, as shown in **Table 4.**

Discussion

This study analyzed the data of patients treated in Thailand's healthcare context. The study showed no difference between the service and medical expenses. This differs from foreign countries because services were provided mainly by nonprofit agencies in Thailand, such as the cost of bone donor services and disinfection and storage, not including inpatient expenses. This study represented medical service data relevant to real-life situations in Thailand.

This data set concluded no difference in the patient's demographic data including age, sex, diagnosis and skills and the choice of reconstruction method after tumor resection. Then it could imply an important cost factor suitable for each patient, affecting different treatment outcomes. This study emphasized the QALY, which was obtained from various factors such as the use of postoperative

Table 4. Sensitivity analyses of price-discounted endoprosthetic reconstruction

Situation	Cost (Baht)	QALY gain
Price Discounted for Balance Utility		
Substitute Osteoarticular Allograft	106,408.55 (↓55.37%)	12,518.65 (5.40%N*)
Substitute Recycled Bone Autograft	125,408.55 (↓47.16%)	14,823.08 (6.40%N*)
Substitute Various Biologic Reconstruction	118,811.81 (↓50.17%)	13,977.86 (6.00%N*)
Price Discounted by 15%		
Substitute Osteoarticular Allograft	202,667.49 (↓15.00%)	39,257.25 (16.90%N*)
Substitute Recycled Bone Autograft	202,667.49 (↓15.00%)	32,248.38 (13.90%N*)
Substitute Various Biologic Reconstruction	202,667.49 (↓15.00%)	34,430.47 (14.80%N*)
Price Discounted for use 20% of N*		
Substitute Osteoarticular Allograft	228,496.67 (↓4.00%)	46,432.02 (20.00%N*)
Substitute Recycled Bone Autograft	265,075.50 (↓----%)	46,432.02 (20.00%N*)
Substitute Various Biologic Reconstruction	251,873.85(↓----%)	46,432.02 (20.00%N*)

N: NESDC Economic Report 15th August 2022; Office of the Economic and Social Development Council, Thailand

organs, pain, anxiety and overall satisfaction. All collected data were displayed as the utility value. Moreover, these data also indicated the treatment complications. The allograft reconstruction had the most complications of infection and system failure, resulting in patients undergoing repeated surgery, including amputation. The recycled autograft surgery had complications of undergoing revision surgery. All these complications were included in the utility analysis. The data suggested that the surgery with the endoprosthetic reconstruction method exhibited the highest utility value, meaning the patient was most satisfied with the treatment involving endoprosthetic reconstruction. In addition, a low complication rate was observed using this surgical method. The surgical expense of allograft reconstruction was lower than that of endoprosthetic reconstruction; therefore, the cost-effectiveness assessment in cost-utility showed that allograft reconstruction was the most cost-effective, followed by recycled autograft. Even though allograft reconstruction indicated the lowest cost, recurrent disease occurred. Because the recurrent illness was a significant complication affecting well-being postoperation among patients, this surgical method was not cost-effective in terms of QALY.

This study also investigated the development opportunity for surgery-based methods because the endoprosthesis reconstruction presented the highest utility value and the fewest complications from treatment. Therefore, the QALY gain of this method was calculated. Comparing the other surgical methods that were more cost-effective, developing surgical methods by endoprosthesis reconstruction was as cost-effective as the allograft reconstruction method, which was the most cost-effective, with the additional investment required per QALY in the amount of 49,191.93 THB, the same as the other biologic reconstruction treatments. In **Table 4**, when the cost of endoprosthesis reconstruction decreased by 55.37% at 106,408.55 THB, allograft reconstruction would be as cost-effective as the most cost-effective surgical method. However, reducing those costs by 15% at 202,667.49 THB required the additional investment for a QALY gain of only 39,257.25 THB or only 16.9% of the average Thai per capita in 2021, according to the announcement in the 2022 economic projections of the Office of the National Economic and Social Development Council August 15, 2022 (NESDC Economic Report 15th August 2022; Office of the Economic and Social Development Council, Thailand).[11] Reducing costs by only 15%

would make the most cost-effective treatment method compared with the cheapest technique, recycled autograft. Therefore, additional investment for a QALY of only 13.9% of the average Thai per capita would be required. When starting with Thai per capita, if we invest more for an additional QALY gain at 2% of the average income of Thai per capita or 46,432.02 THB, the endoprosthesis reconstruction cost was required to drop by 4% or 228,496.67 THB. This data suggested that we could use this surgical method instead of the most cost-effective technique, allograft reconstruction. This additional investment benefits a patient who has undergone surgery to be healthy after surgery, without risk of complications from allograft reconstruction surgery. It could also reduce the cost of treating complications.

Conclusion

Endoprosthesis reconstruction presented the highest utility value with high patient satisfaction and minimal complications. Employing this method at the total price could replace the most cost-effective technique, allograft reconstruction, but required an additional investment for the QALY gain of 39,257.25 THB, or only 16.9% of the average income of Thai per capita. Reducing the surgery price by only 15% when the investment was only 32,248.38 THB, or only 13.9% of the average Thai per capita would permit using this method instead of the cheapest operation, recycled autograft. In addition, when we invest 20% of the average income of Thai per capita or 46,432.02 THB, the endoprosthesis reconstruction cost will drop by 4%. This surgical method would be comparable with the most cost-effective technique, allograft reconstruction.

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INCIDENCE AND RISK FACTORS FOR RAPID DECLINE OF PRESERVED ESTIMATED GLOMERULAR FILTRATION RATE AMONG PATIENTS WITH HYPERTENSION IN A COMMUNITY HOSPITAL

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Abstract

Background: Hypertension is the second most common leading cause of chronic kidney disease. Related studies explored the causes of the rapid decline of kidney function in advanced kidney disease. However, the causes of the rapid decline of kidney function in the early stage or preserved function of hypertension-related kidney disease are less evident.

Objectives: The study aimed to identify the incidence and associated risk factors for the decline of the glomerular filtration rate (GFR) among patients with hypertension with preserved kidney function, estimated GFR (eGFR) above 60/mL/min/1.73m^2, at a community hospital.

Methods: A retrospective cohort study was conducted among patients with hypertension with 2 eGFR measures at least 1 year apart and were identified from all cases attending at the Outpatient Department, Sanam Chai Khet Hospital, Chachoengsao Province. The incidence of the estimated rate of eGFR decline greater than 5 mL/min/1.73m^2 yearly (ERGFR5/yr) was determined. In addition, potential risk and protective factors were identified using Poisson Regression.

Results: Of 1,328 patients with hypertension, 53.05% were females. The mean age was 59.68 ± 11.58 years. The mean GFR measure at the 1st visit was 88.71± 14.73 mL/min/1.73m^2. The incidence of ERGFR5/yr was 11.1 (95% CI: 10.1-12.3)) per 100-person year. Risk factors were being 60 years or older with an incidence rate ratio (IRR) of 1.4 (95% CI: 1.11-1.77), having diabetes mellitus with an IRR of 1.67 (95% CI: 1.37-2.04) and uncontrolled hypertension with an IRR of 1.15 (95% CI: 1.10-1.20).

Conclusion: The incidence of ERGFR5/yr among renal preserved patients with hypertension was relatively low compared with other studies. Aggressive intervention among patients with comorbidity could reduce the incidence of rapid decline in eGFR.

Keywords: Hypertension, Rapid decline kidney function, Incidence, Risk factors

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Introduction

Hypertension is one of the most problematic noncommunicable diseases affecting millions of people around the world.[1] Moreover, hypertension leads to premature morbidity and mortality. It has been forecasted that by 2025, the prevalence of hypertension will rise to 1.56 trillion people worldwide. In developing countries, the prevalence may be as high as 80%.[1, 2] Hypertension also predisposes the patient to develop other chronic diseases such as cerebrovascular disease, heart failure, cardiovascular diseases, peripheral arterial disease and chronic kidney diseases; thus, leading to premature morbidity and mortality.[1,2] In 2014, data from the National Health Examination Survey V suggested that hypertension affects nearly one in five individuals. Unfortunately, the overall prevalence of hypertension among Thai individuals older than 15 years had increased from 17% in 1992 to 24.7% in 2014.[3] Furthermore, another study found that the prevalence of uncontrolled hypertension in Thailand was around 25%.[4] In 2009, the National Health Examination Survey IV reported that 25.4% of Thai individuals were hypertensive. [5, 6]

Chronic kidney disease (CKD) is another common noncommunicable chronic disease in Thailand with a prevalence of around 20%. [7, 8] CKD management incurs a high healthcare cost, especially in end-stage kidney disease when dialysis or kidney transplantation is needed.[9] Combined eGFR, albuminuria and other factors may affect the progression of CKD but no guiding bases have been established within therapeutic guidelines. (10)

The glomerular filtration rate (GFR) is the universal concept for assessing kidney function. The GFR is usually estimated with creatinine values because creatinine values remain constant in the case of constant food intact and muscle mass.[11, 12] A rapid decline in estimated GFR (eGFR) means having an eGFR that decreases more than 5mL/min/1.73² yearly may predict the progression of worsening kidney function among patients with CKD. (11, 13, 14) Later on, the terminology of rapid decline in eGFR is used to describe the nature of eGFR decline in a patient already receiving a diagnosis of CKD to predict a poor prognosis. [15]

Diabetes and hypertension are the leading etiologies of CKD.[9] To determine what factors led to decreased kidney function among patients with hypertension, this study aimed to identify risk factors for eGFR decline among patients with hypertension using a cutoff point of >5mL/min/1.73² yearly, like those with CKD. The incidence and risk factors associated with the eGFR declining greater than 5 mL/min/1.73m^2 yearly (ERGFR5/yr) among patients with hypertension who had started eGFR above 60/mL/min/1.73m^2 were studied. Factors investigated were comorbidities i.e., diabetes mellitus, dyslipidemia, cerebrovascular diseases, cardiovascular disease and arthritis including gout. Occupation, history of smoking and alcohol consumption were also recorded. Results could be used to prevent further decline in kidney function among patients with hypertension having preserved kidney function. [14, 19, 20]

Methods

Study population

A retrospective cohort study was conducted at a community hospital, Sanam Chai Khet Hospital, Chachoengsao Province. The Institutional Review Board of the Royal Thai Army approved the study with the identification code M030h/64. The eligibility criteria for patients were 18 years and older who were hypertensive with at least two creatinine levels taken more than one year apart from 2011 to 2021. Moreover, the baseline eGFR was more than 60 mL/min/1.73m². Patients who were pregnant or meeting the criteria for acute kidney injury (AKI) using Kidney Disease Improving Global Outcomes (KDIGO) were excluded from the study.

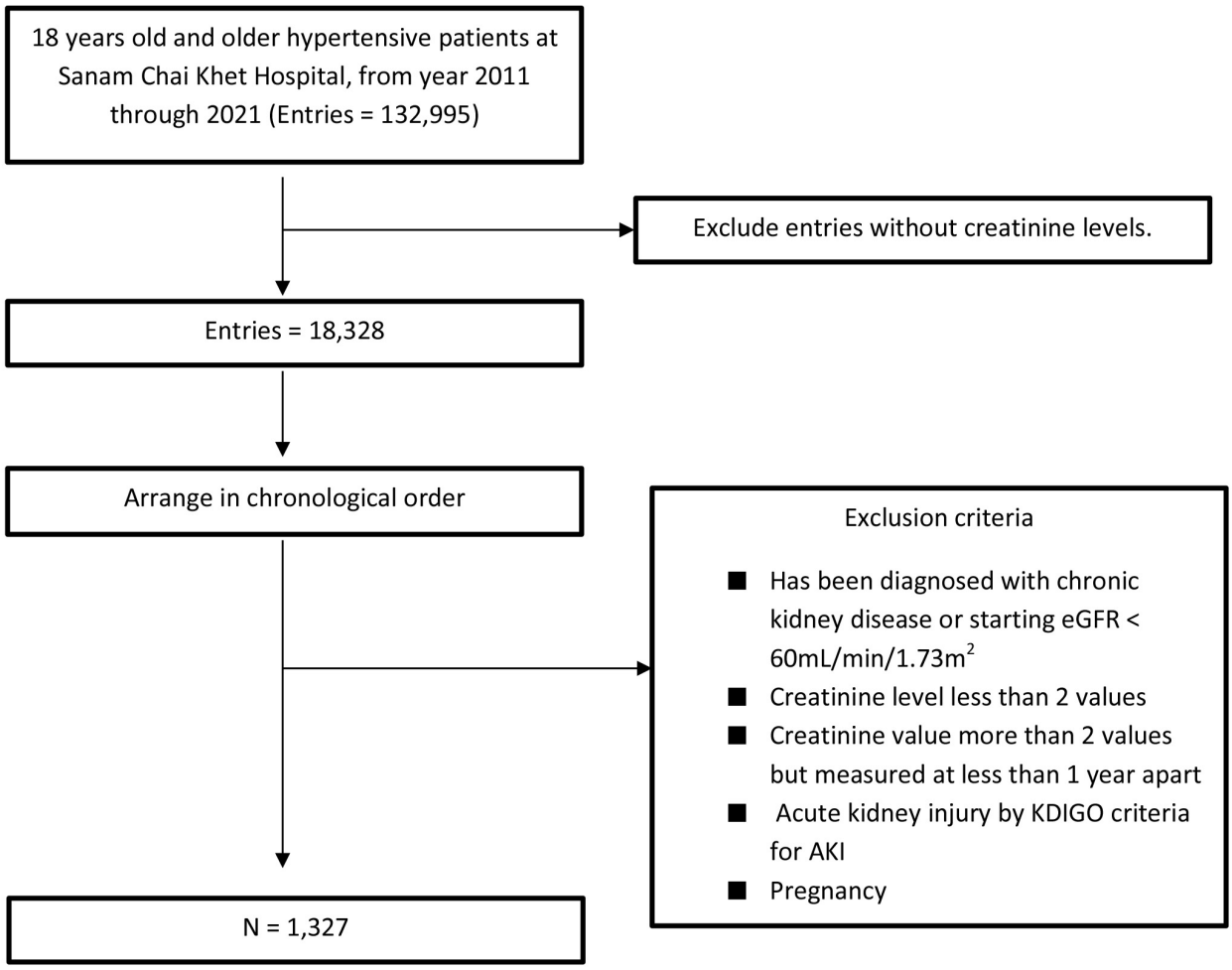

Figure 1. Flowchart for selection of patients in the study

Data collection

From 2011 to 2021, data were collected from patient's medical records at Sanam Chai Khet Hospital. According to ICD-10, cases with hypertension (I10) were extracted from the database along with demographic characteristics, comorbidity, body weight and height and baseline systolic and diastolic blood pressure. Patients were screenednusing inclusion and exclusion criteria as described in **Figure 1**. Of 132,997 OPD visits, thosewithout creatinine levels were excluded, down to 18,330 OPD visits. Then we excluded patients presenting creatinine levels <60 mL/min/1.73m², those with creatinine levels less than one year apart and those with acute kidney injury using KDIGO criteria and pregnancy using ICD10 (Z34), respectively.

Other covariates were extracted; cardiovascular disease included ischemic heart disease (I25-). Cerebrovascular diseases included I63-, I67-, I68- and I69-. Arthritis included gouty arthritis and osteoarthritis that might be exposed to the use of NSAID (M10- and M06-). Furthermore, atrial fibrillation included those that received a diagnosis of ICD10 (I48-).[16] In this study, creatinine levels were determined using the enzymatic method. The CKD-EPI formula from "The Nephrology Society of Thailand" in 2018 was used to calculate. A rapid decline in eGFR was defined as greater than 5 ml/min/1.73m² yearly using the KDIGO criteria.[17] The rate equation used to calculate the estimated decline rate of eGFR is shown below.

Sex	Creatinine level mg/dL	Equation
Female	≤0.7	$GFR = 141 \times \left(\frac{SCr}{0.7}\right)^{-0.329} \times 0.993^{Age}$
	>0.7	$GFR = 141 \times \left(\frac{SCr}{0.7}\right)^{-1.209} \times 0.993^{Age}$
Male	≤0.9	$GFR = 141 \times \left(\frac{SCr}{0.9}\right)^{-0.329} \times 0.993^{Age}$
	>0.9	$GFR = 141 \times \left(\frac{SCr}{0.9}\right)^{-0.329} \times 0.993^{Age}$

$$\frac{eGFR_{creatinine\ visit\ 2} - eGFR_{creatinine\ visit\ 1}}{days\ between\ visit\ 1\ and\ 2 \Big/ 365}$$

Statistical analysis

STATA14 was used to determine descriptive statistics of the baseline characteristics and demographic data.[18] Continuous data were classified into ordinal scales such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) and baseline eGFR. Likewise, the categorical data such as occupation, smoking and alcohol consumption was presented as a percentage.

Using multiple Poisson regression, adjusted relative risks, 95% Confidence Interval (CI), and p-values were determined. Each potential risk factor was adjusted for sex, age group, occupation, smoking status, alcohol status, BMI, diabetes, dyslipidemia, cardiovascular disease, atrial fibrillation, gout, osteoarthritis, cerebrovascular disease, baseline eGFR groups, and SBP and DBP groups. The risk factors were identified using IRR and 95% CI. For survival analysis, the study time was from October 2011 to October 2021. Right censoring was performed when the patient did not achieve the rate of rapid decline eGFR <5 mL/min/1.73m^2 until the end of the follow-up. The person-time calculated comprised the observation time until the event occurred, presumably the end time at which the mean eGFR was >5 mL/min/1.73m^2.

RESULTS

Clinical characteristics

A total of 1,326 patients with hypertension and serial eGFR values at least one year apart were included in the analysis. For the baseline characteristics, 53.1% were female and the mean age was 59.7 ± 11.5 years **(Table 1).** Of these, 21.2% smoked and 23.4% consumed alcohol. For BMI, 10.3% were underweight (BMI<18 kg/m²), 24.2% presented normal BMI (18 to 22.9 kg/m²) and 65.5% were obese (BMI >23 kg/m²). Among all patients with hypertension and preserved kidney function, 29.2% had diabetes mellitus. Other comorbidities comprised 49.0% dyslipidemia, 4.2% cardiovascular disease, 3.2% arthritis, 1.6% atrial fibrillation and 4.8% cerebrovascular diseases.

Incidence of ERGFR5/yr and hypertension

The incidence of ERGFR5/yr among renal preserved patients with hypertension was 11.1 person per 100 person-year (95% CI: 10.1-12.3) with a mean follow-up time of 1.7 years **(Table 1).** The rate of decline in eGFR yearly was 0.65 units yearly (95% CI: 0.34-0.96).

Risk factors for developing ERGFR5/yr

The study showed that age 60 years or older was associated with ERGFR5/yr with an adjusted IRR of 1.40 (95% CI: 1.11 to 1.77). Moreover,

having diabetes mellitus was associated with a rapid decline in eGFR with an adjusted IRR of 1.67 (95% CI: 1.37 to 2.04). On the other hand, having uncontrolled hypertension or blood pressure ≥140/90 mmHg was associated with developing ERGFR5/yr with an IRR of 1.15 (95% CI: 1.10 to 1.20).

DISCUSSION

The incidence of ERGFR5/yr was 11.1 person per 100 person-year among patients with hypertension and GFR above 60 mL/min/1.73m^2, with a mean follow-up time of 1.7 years. This constituted the first study investigating the incidence and risk factors of ERGFR5/yr among patients in this community hospital. We identified modifiable and nonmodifiable risk factors for eGFR decline. Our study reported that the risk factor of ERGFR5/yr was uncontrolled hypertension greater than 140/90 mmHg similar to the study by Bai et al.; the rapid decline of eGFR was associated with systolic hypertension.[12] Other related studies found that diabetes was associated with a rapid decline in kidney function.[19, 20] Similarly, in our study, those with diabetes and hypertension were more likely to develop ERGFR5/yr. However, dyslipidemia and atrial fibrillation did not show any association with ERGFR5/yr. In contrast to related studies, dyslipidemia was associated with a rapid decline in kidney function.[21] Other related studies showed that among patients already receiving a diagnosis of CKD; the incidence was lower than among those in China where a 23.9% cumulative incidence of rapid decline eGFR among elderly patients with hypertension was reported.[11, 22]

Table 1. General characteristics of patients with hypertension with preserved kidney function and incidence of rapid decline eGFR

Characteristic	
N	1326
Sex	
Female	704 (53.1)
Male	622 (46.9)
Age (y)	59.7±11.5
≤60	693 (52.3)
>60	633 (47.7)
Smoking	
No	1045 (78.8)
Yes	281 (21.2)
Alcohol Cption	
No	1015 (76.6)
Yes	311 (23.4)
Body Mass Index	
<18	136 (10.3)
18-22.9	321 (24.2)
≥23	869 (65.5)
Diabetes	
No	939 (70.8)
Yes	387 (29.2)
Dyslipidemia	
No	676 (51.0)
Yes	650 (49.0)

Table 1. General characteristics of patients with hypertension with preserved kidney function and incidence of rapid decline eGFR (Cont.)

Characteristic	
Cardiovascular disease	
No	1271 (95.9)
Yes	55 (4.2)
Atrial Fibrillation	
No	1305 (98.4)
Yes	21 (1.6)
Arthritis	
No	1283 (96.8)
Yes	43 (3.2)
Cerebrovascular disease	
No	1262 (95.2)
Yes	64 (4.8)
Baseline eGFR	
≥90	634 (47.8)
60-89.9	692 (52.2)
BP ≥ 140/90 mmHg	
No	381 (28.7)
Yes	945 (71.3)
FBS >180mg/dL	
No	1172 (88.4)
Yes	154 (11.6)
TG≥150 mg/dL	
No	629 (63.4)
Yes	363 (36.6)
LDL≥100mg/dL	
No	265 (29.1)
Yes	645 (70.9)
Median follow-up time, years (IQR)	1.7 (1.1-2.2)
Outcomes	
Person-years of exposure	3403
Number of events	379
Incidence rate /100 person-years (95%CI)	11.1 (10.1-12.3)
Rate decline eGFR per year (ml/min/1.73m^2/year)	0.65 (0.34-0.96)

The related study found that chronic kidney progression was associated with higher levels of nonHDL cholesterol in the blood.[23] In contrast to this study, our patients had received lipid-lowering agents. In addition, long term medication to treat noncommunicable diseases ultimately played an important role in kidney function. On the other hand, among patients with atrial fibrillation, studies compared the effects of nonvitamin K antagonist oral anticoagulant (NOAC) and warfarin; NOAC provided more reno-protective effects than warfarin.[24-26] Therefore, further investigation regarding drug use is crucial for establishing a solid conclusion.

Table 2. Multiple Poisson Regression analysis of incidence and risk factors of rapid renal progression among patients with hypertension

	Person-years of exposure	Number of events	Incidence rate /100 person-years (95%CI)	Crude IRR (95%CI)	*p*-value	Adjusted IRR (95%CI)	*p*-value
Sex							
Female	1579	201	12.7 (11.1-14.6)	1		1	
Male	1824	178	9.8 (8.4-11.3)	0.99 (0.65-1.52)	0.965	1.10 (0.67-1.81)	0.716
Age (years)							
≤60	1829	169	9.2 (7.9-10.7)	1		1	
>60	1574	210	13.3 (11.7-15.3)	1.39 (1.30-1.49)	<0.001	1.40 (1.11-1.77)	0.004
Smoking							
No	2705	297	11.0 (9.8-12.3)	1		1	
Yes	698	82	11.8 (9.5-14.6)	1.03 (0.95-1.11)	0.473	1.05 (0.63-1.74)	0.850
Alcohol Consumption							
No	2614	287	11.0 (9.8-12.3)	1		1	
Yes	789	92	11.7 (9.5-14.3)	1.02 (0.95-1.10)	0.599	0.94 (0.39-2.23)	0.881
Body Mass Index							
<18	387	40	10.3 (7.6-14.1)	1		1	
18-22.9	796	102	12.8 (10.6-15.6)	1.08 (0.73-1.58)	0.701	1.19 (1.15-1.23)	<0.001
≥23	2221	237	10.7 (9.4-12.1)	0.94 (0.74-1.19)	0.604	1.25 (1.07-1.45)	0.005
Diabetes Mellitus							
No	2436	227	9.3 (8.2-10.6)	1		1	
Yes	967	152	15.7 (13.4-18.4)	1.73 (1.27-2.36)	<0.001	1.67 (1.37-2.04)	<0.001
Dyslipidemia							
No	1727	173	10.0 (8.6-11.6)	1		1	
Yes	1676	206	12.3 (10.7-14.1)	1.33 (0.95-1.86)	0.092	0.92 (0.62-1.35)	0.666
Cardiovascular disease							
No	3278	365	11.1 (10.1-12.3)	1		1	
Yes	126	14	11.1 (6.6-18.8)	0.97 (0.40-2.35)	0.955	1.27 (0.28-5.77)	0.754
Atrial Fibrillation							
No	3345	375	11.2 (10.1-12.4)	1		1	

able 2. Multiple Poisson Regression analysis of incidence and risk factors of rapid renal progression among patients with hypertension (Cont.)

	Person-years of exposure	Number of events	Incidence rate /100 person-years (95%CI)	Crude IRR (95%CI)	*p*-value	Adjusted IRR (95%CI)	*p*-value
Yes	58	4	6.8 (2.6-18.2)	0.60 (0.46-0.77)	<0.001	0.35 (0.08-1.55)	0.165
Arthritis							
No	3268	368	11.3 (10.2-12.5)	1		1	
Yes	135	11	8.2 (4.5-14.7)	0.80 (0.66-0.98)	0.030	1.04 (0.88-1.24)	0.621
Cerebrovascular disease							
No	3239	358	11.1 (10.0-12.3)	1		1	
Yes	164	21	12.8 (8.3-19.6)	1.14 (0.83-1.57)	0.414	1.52 (1.06-2.19)	0.023
Baseline eGFR							
≥90	1589	176	11.1 (9.6-12.8)	1		1	
60-89.9	1815	203	11.2 (9.7-12.8)	1.10 (0.94-1.28)	0.225	1.22 (0.88-1.70)	0.228
BP ≥ 140/90 mmHg							
No	943	117	12.4 (10.4-14.9)	1		1	
Yes	2460	262	10.6 (9.4-12.0)	0.92 (0.91-0.93)	<0.001	1.15 (1.10-1.20)	<0.001
FBS >180mg/dL							
No	3013	308	10.2 (9.1-11.4)	1		1	
Yes	391	71	18.2 (14.4-22.9)	1.71 (1.43-2.03)	<0.001	1.18 (0.91-1.52)	0.220
TG≥150 mg/dL							
No	1607	171	10.6 (9.2-12.4)	1		1	
Yes	982	108	11.0 (9.1-13.3)	1.05 (0.86-1.28)	0.616	1.06 (0.75-1.48)	0.747
LDL≥100mg/dL							
No	581	82	14.1 (11.4-17.5)	1		1	
Yes	1535	177	11.5 (9.9-13.4)	0.85 (0.83-0.87)	<0.001	0.95 (0.82-1.10)	0.479

ICD 10 for diabetes: E10-E14- , ICD 10 for dyslipidemia: E78- , ICD 10 for cardiovascular disease (ischemic heart disease): I25- , ICD 10 for atrial fibrillation: I48- , ICD 10 for arthritis M10-, M06- and ICD 10 for cerebrovascular disease included I63-, I67-, I68-, I69-

The results of this study agreed with that of Chamnanmont et al.[26] investigating the prevalence and associated factors for the decline of eGFR among patients attending a community hospital and reported the incidence of eGFR<60 mL/min/1.73m^2 was 20.3%; risk factors included age, NSAIDs use and presenting high blood pressure.

In this study, the patients with hypertension exhibited good or mild impaired renal function or a baseline eGFR >60 mL/min/1.73m^2. Early intervention could be used in this particular group as shown that the rate of eGFR was lower compared with other studies that included patients with established CKD. Morbidity and mortality could possibly be reduced long term if we focused on blood pressure control among patients receiving an early diagnosis of hypertension.[26]

This study encountered limitations. Proteinuria data was not included as one of the variables; proteinuria could be a mediator or extraneous variable and used as the main predictor for poor prognosis and increasing rate of kidney function decline. [17, 27] Additionally, proteinuria was also a major biomarker for the diagnosis of early stages of kidney disease.[17] Therefore, the study population included patients with hypertension alone and those with hypertension and CKD I or II. Thus, further investigation is required for a conclusive result.

In this study, certain ICD 10 were excluded, i.e., being pregnant and those with the criteria of AKI by KDIGO definition. However, more substile events that could be lower such as the history of infection or hospital admission between the two OPD visits had not been explored. Of 130,000 patients with hypertension, 1,326 patients had the criteria of having two creatinine levels one year apart and having a baseline eGFR >60%. The study did not eliminate the degree of natural variation of serum creatinine levels which tended to be higher than those with normal creatinine levels. Thus, further study with a larger data pool is required to establish a strong association. This study only determined a rate of decreased eGFR among patients with hypertension and preserved kidney function. However, patients with hypertension and eGFR <60 were not studied in the same setting. Additionally, this study did not include the potential effects of medication in developing rapid decline in kidney function.

CONCLUSION

The incidence of ERGFR5/yr among renal preserved patients with hypertension was 11.1 person per 100 person-year with a mean follow-up time of 1.7 years. Factors positively linked to the ERGFR5/yr included age >60 years, BP >140/90 mmHg and diabetes mellitus. Early intervention for adequate hypertension control and optimal control for diabetes could prevent the decline of eGFR among patients with hypertension and preserve renal function.

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PERIPROSTHETIC JOINT INFECTION AFTER WIDE RESECTION BONE TUMOR AND ENDOPROSTHETIC RECONSTRUCTION IN A PATIENT WITH OSTEOSARCOMA: A CASE REPORT

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Abstract

Bone and connective tissue cancer treatment has been improved to achieve a significant survival rate. Limb salvage surgery, an efficient surgical technique, has been established to preserve limbs. Endoprosthesis reconstruction constitutes an essential part of the treatment method, and the attending medical team requires knowledge to reduce the side effects of this operation. The consequential infection is a common complication, often leading to worse use of the limbs when finishing the treatment. This report describes a patient presenting an infection in a prosthesis after endoprosthesis reconstruction using a limb salvage surgery technique. Due to the comprehensive resection surgery, the typical structure has been significantly damaged, which could lead to a high risk of neurovascular structure damage during adequate debridement and lead to the need for amputation. Thus, the decision to treat an infection resulted in patients undergoing multiple surgeries and reducing their functional outcomes until crucial. These patients should be carefully monitored to prevent infection and obtain a good quality of life in the long term.

Keywords: Endoprosthesis reconstruction, Periprosthetic joint infection

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Introduction

Bone sarcoma is a common cancer that can affect people at any age. Approximately 50% of bone cancer is diagnosed among people under the age of 35 years and is more often found on the limbs than in other regions, with about one half coming across the bones around the knee.[1, 2] The treatment among patients with bone sarcoma affects movement, walking, routine activity in daily life and quality of life in the long term. In the past, treating bone sarcoma has shown a progressive improvement achieving better survival rates. The decrease in amputation treatment can increase limb salvage surgery. However, the survival rate and postoperative disease-free status showed no difference.[3] As limb salvage surgery requires knowledge of reconstructive surgery, a method has to be provided to affect patients' quality of life positively.[4] One such method is endoprosthesis reconstruction allowing the patient to return to everyday life as quickly as possible. On the other hand, side effects can occur using this surgical method. Endoprosthesis reconstruction treatment, including infections, can occur at the rate of up to 8.5% in distal femoral replacement and 16.8% in proximal tibial replacement.[5] This study reports the infection problem in a patient with endoprosthesis reconstruction. It comprises an essential issue, though found infrequently, because it directly affects patients' treated outcomes and quality of life. The infection issue can be solved in many ways including increasing the duration of patient administration of antibiotics while in the hospital, needing repeated surgery, and may result in the patient undergoing an amputation.[6]

Case report

The patient was a 31-year-old single woman. Before visiting the hospital, she recognized a mass in the right knee, and a slow-moving lump was felt in the right knee two months earlier. She was slightly uncomfortable and did not fully move, especially in flexion. She denied havingother symptoms, including nocturnal discomfort, anorexia, weight loss and any history of underlying sickness, no history of drug use, alcohol consumption or smoking. A history of ibuprofen and diclofenac allergies were known occurrences.

The physical examination revealed a 7-cm diameter mass that was palpable at the small area of the left knee. The mass was hard in substance, fixed to the bone, did not hurt, presented a rough surface, was poorly circumscribed and showed no pulsatile activity. No wounds or unusual skin lesions were present. The left knee's range of motion was 0 degrees at full extension and 110 degrees at full flexion. The popliteal, posterior tibial, and dorsalis pedis were pulsatile at a regular rate and rhythm. At the left groin and left lower extremity, the lymph node was not palpable.

Plain X-ray AP and lateral views of the left knee showed the lesion at the metaphysics-diaphyseal junction region of the distal left femur; it involved a mixed osteoblastic and osteolytic lesion with an uneven moth-eaten kind of boundary, as shown in **Figure 1.** Soft tissue development and periosteal sunburst reaction were observed. The osteoid matrix type was identified, and no significant pathologic fracture was observed.

Using Magnetic Resonance Imaging (MRI), the plain X-ray revealed a bone lesion and parosteal osteosarcoma was suspected. The other investigation showed no sign of visceral organs or bonny metastases, and the core needle biopsy showed a low-grade spindle cell tumor detected by core needle biopsy. Murine double minute 2 (MDM2) strain was positive, supporting the diagnosis of parosteal osteosarcoma.

A wide excision was performed on the left femur by removing the suspected cancerous area and adjacent normal or healthy tissue margins to remove all cancer and repair using an endoprosthesis. According to the histopathology investigation, the largest dimension of the dedifferentiated posterior osteosarcoma with posterior boundary at the medial and posterior border was 9 cm. After surgery, the patient underwent four cycles of chemotherapy with cisplatin, doxorubicin and 70 grays of external radiation therapy. The patient responded well to treatment, with no recurrence or metastasis detected in other organs. Furthermore, the patient expressed satisfaction with the functioning of the right knee.

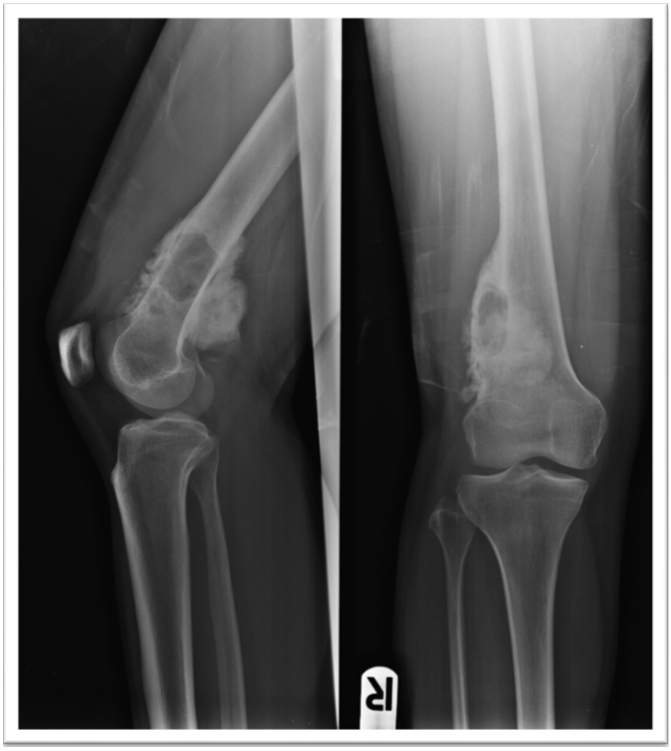

Figure 1. Mixed osteoblastic and osteolytic lesions with an irregular moth-eaten border at the metaphysic-diaphyseal junction area of the distal of the left femur are shown. Sunburst periosteal reaction and soft tissue production are observed. The matrix comprised osteoid type identified from plain X-ray.

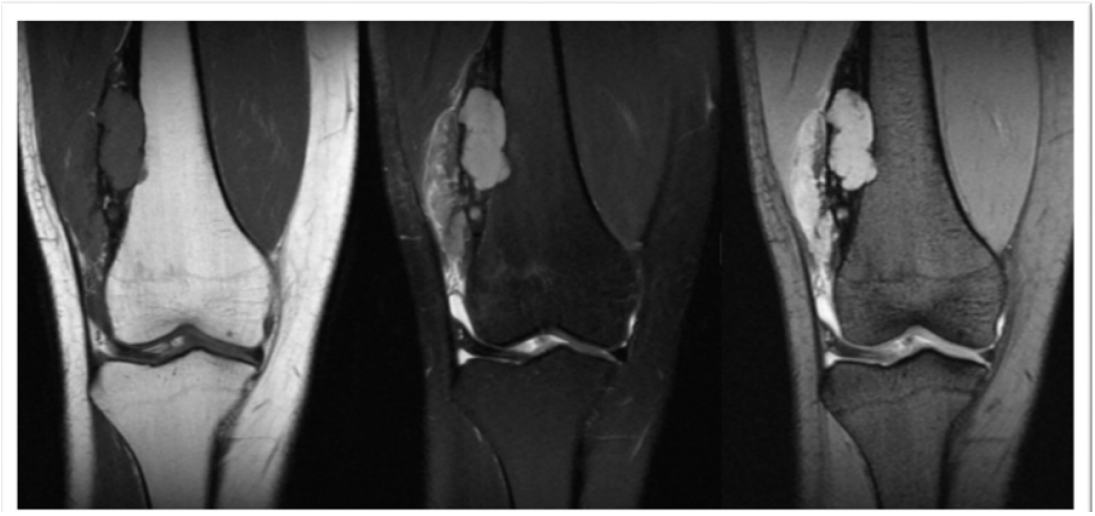

Figure 2. MRI shows suspected parosteal osteosarcoma, irregular mass on the postero-lateral cortex of the right distal femur and invasion of the medullary-trabecular component with hypointense on T1 and hyperintense signal on T2 intensity with peripheral soft tissue edema.

On 14-12-2019, the patient was involved in a car accident two years later. The left knee was crushed, resulting in an abrasion wound over the prosthesis area. The patient reported warm, red, swollen and painful symptoms. The knee examination showed a positive ballottement sign representing increased intra-articular fluid. During the arthrocentesis, 180 mL of pus was found. Subsequently, an arthrotomy was conducted to debride the left knee and perform polyethylene exchange.[6] Tissue samples were sent for laboratory examination. The hemoculture bottle used for tissue culture demonstrated a positive result for *Escherichia* coli but was negative

for *Staphylococcus coagulase*. The histologic investigation did not reveal any evidence of recurring malignancy.

In cases where the pathogen cannot be identified, antibiotics are prescribed based on suspected infecting organisms to ensure broad coverage against potential pathogens. Identification of the specific pathogen may be hindered by various reasons, such as the techniques used for specimen collection. Nonetheless, every effort was made to maximize the accuracy of pathogen identification.[6] This patient received the following antibiotics medications: 2 gm of ceftriaxone intravenous once daily: 14 to 23 December 2019, 500 mg of metronidazole intravenous every 8 hours: 14 to 23 December 2019, 2.2 gm of augmentin intravenous every 12 hours: 24 December 2019 to 4 January 2020, 400 mg of ciprofloxacin intravenous every 8 hours: 4 to 0 January 2020 and 500 mg of ciprofloxacin per oral twice daily: 30 days after that infection subsided. The evaluation of infection subsiding was determined by improvements in patient symptoms and laboratory test results indicating a decrease in inflammation including reduced white blood cell count, particularly neutrophils and decreased inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

On 08-08-2020, eight months later, the patient complained that her knee had returned to warm, red, swollen and painful. The periprosthetic infection was identified by laboratory examination. The blood test revealed a white blood cell count of 18,000 cells/mL, with 82% polymorphonuclear leukocytes (PMN). The ESR was 114 mm/hr, and the CRP level was 98 mg/dL. Additionally, synovial fluid analysis showed a white blood cell count of 90,000 cells/mL, with 98% PMN. No organisms were detected in the joint fluid. The patient initially received conservative treatment with 400 mg of ciprofloxacin intravenously every 8 hours from 8 August 2020 to 5 December 2020. However, due to the clinical evaluation and laboratory test results indicating the persistence of infection, the patient required extended intravenous antibiotic therapy. Therefore, she was prescribed 200 mg of rifampicin twice daily for 90 days and 500 mg of ciprofloxacin orally twice daily for 140 days.

On 21-06-2021, ten months later, the first-stage revision of the endoprosthesis was carried out, involving the complete removal of the prosthesis device and its replacement with an antimicrobial cement spacer. A standard surgical intervention for the first-stage revision was recommended to treat periprosthetic infection, even without prosthetic loosening. This was accomplished

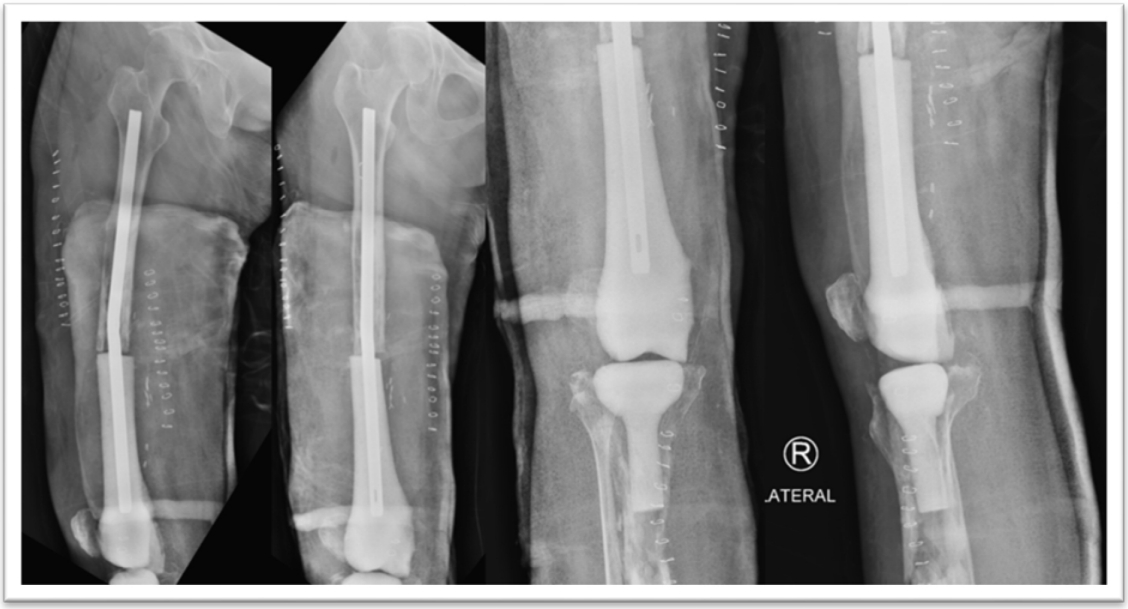

Figure 3. After 1ST stage revision endoprosthesis, radiography was performed by removing the prosthesis and replacing it with an antibiotic cement spacer.

to eliminate any potential source of infection originating from the prosthesis itself. [6] For this procedure, Palacos® cement, containing 0.8 gm of gentamicin and 0.5 gm of gentamycin sulfate, was mixed with 2 gm of vancomycin powder. The surgical technique employed an intramedullary Kuntscher nail to secure the cement spacer to the remaining femur. Due to limited space on the tibia side, additional fixation was not required because surrounding soft tissue solely supported the cement spacer. The patient received 400 mg of ciprofloxacin intravenously every 8 hours from 21 June 2021 to 28 July 2021.

On 25-06-2022, one year later, the infection subsided. The second stage revision endoprosthesis was performed with wound coverage from the medial gastrocnemius muscle flap and split-thickness skin graft. The tissue analysis revealed that the tissue removed from the tibial portion of the bone tested positive for high grade conventional osteosarcoma but negative for bacterial culture. Afterward, the patient received 500 mg of ciprofloxacin twice daily for one month. After the surgery, the patient was ready to receive adjuvant chemotherapy.

On 16-10-2022, four months later, the patient presented at the Emergency Department with signs of a right knee infection and a skin tract on the front of the right leg. The treatment was designed to remove the prosthesis and perform debridement. The intra-operative testing revealed 200 mL of pus around the prosthetic mechanical tube. Pus and tissue were sent to the laboratory for examination, and a cement spacer was applied as a temporary replacement.

After the patient underwent surgery, she received 400 mg of ciprofloxacin intravenously every 8 hours from 16 October to 16 November 2022. She also received 200 mg of rifampicin twice daily and 500 mg of ciprofloxacin orally twice daily for 140 days following that. According to the pus culture, Staphylococcus coagulase was identified that was sensitive to this antibiotic. Various symptoms and laboratory indicators showed an improvement in the infection. The surgical wound was closed tightly without pus, only occasional serum oozing discharge. The patient was evaluated to ensure that the infection was resolved entirely before proceeding with the second-stage surgery.

Discussion

The complications of endoprosthesis reconstruction can occur in several forms, but every study reported that infection was a devastating complication leading to repeat surgery among patients treated with this procedure. Berger et al. [7] found that the primary cause that resulted in repeated surgery among patients with

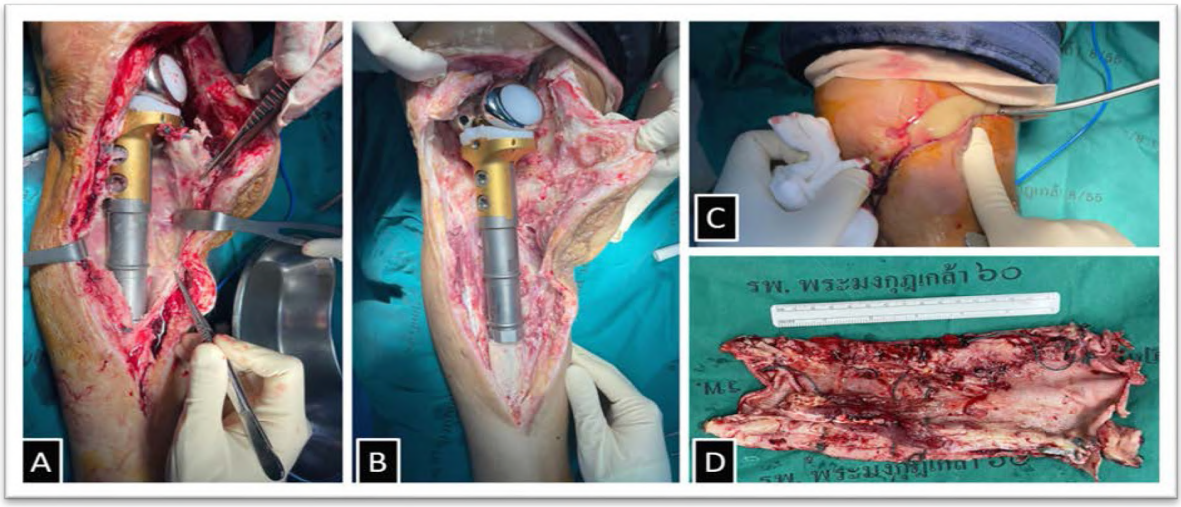

Figure 4. Signs of infection from intra-operative A&B: pus was observed around the prosthesis at the proximal tibia, and a sinus tract leading to the distal femur was also identified. C: pus drainage from the thigh wound. D: the surgical prosthetic tube was removed.

endoprosthesis reconstruction was infection (22%) and soft tissue failure (13%). In contrast, the causes of aseptic release, mechanical failure and tumor recurrence were fewer than the above reasons. The conclusion of this study reported that 17% of patients presenting the complication were no longer able to use the replacement endoprosthesis. Moreover, the study by Zan and colleagues showed that 30% of patients receiving endoprosthesis reconstruction for deep infection experienced recurrence infections that may have required re-surgery or led to amputation. Zajonz et al.[9] also found similar data that these events occurred in 37% of cases. This finding was consistent with Zajonz et al. reporting the data on 37% of such events.[9]

Several studies provided similar information about the pathogens. In 1984, Klenerman[10] determined that 75% of those patients were infected with gram-positive bacteria consisting of Staphylococci (40-45%) and gram-positive anaerobes or micro-aerophilic organisms (30-35%). Gram-negative anaerobes bacteria were rarely found. Only Escherichia coli or Pseudomonas sp. were found, similar to the study of Zajonz et al.[9] in 2016, even though the reports are 32 years apart.

The validity of the diagnostic criteria is crucial because the treated outcomes will directly affect the quality of life of such patients. Tsukayama et al.[11] classified the characteristics of pathogen infection after endoprosthesis reconstruction and applied them to patients experiencing joint replacement after surgically removing the bone sarcoma. The Tsukayama classification divided pathogen infection in four categories as follows, type I; positive culture of intra-operative samples with no previous indication of infection, type II; early infection: onset of symptoms within one month, type III; chronic infection: symptoms after one month and type IV; acute hematogenous infection.

This case was classified as a type 4 pathogen infection because the infection was detected two years after surgery. The initial symptoms when the patient met a doctor indicated an infection in a joint replacement after surgery. After aspirating from the knee joint, 180 mL of pus was found. Then this patient received antibiotic treatment, NS the required surgical pus drainage, joint lavage and excision of dead tissue (arthrotomy and debridement). From the Tsukayama and college recommended guidelines[13], the surgical treatment for joint lavage in acute hematogenous infection should remove the polyethylene inserts. However, polyethylene removal among patients with an endoprosthesis may be delayed because it requires special equipment. Therefore, the medical team consulted with the patient and agreed concurrently that all parts of the endoprosthesis must be retained in the first round of surgery, then treated with antibiotics to inactivate any infection. After the surgery, the medical team administered the treatment providing six weeks of intravenous and oral antibiotics for four weeks until the infection subsided. Although the patient exhibited symptoms suggesting a re-infection of the prosthesis ten months later, the synovial fluid test did not detect any infection. The patient received additional intravenous and oral antibiotics and cotreatment with rifampicin[12, 13], expecting to reduce Staphylococcal biofilm. In this case, the patient's symptoms indicated severe inflammation and purulence in the joint, but the exact pathogen could not be identified. Therefore, administering broad-spectrum antibiotics became necessary to cover all possible infectious agents and limit the spread of infection. In the absence of definitive pathogen identification, the physician relied on the assumption that Staphylococcus species were likely, despite the potential for errors in the identification process.

The medical team consulted about the patient's treatment plan and agreed concurrently to suggest the patient continue using that prosthesis joint with avoiding the revision arthroplasty because the repeated surgery and prolonged length of stay would seriously affect the quality of life of working-age patients. The period after infection and treatment in this patient was about one year. The physical examination and laboratory tests revealed a recurrent infection in the prosthesis; accordingly, the medical team and patient concurred that surgery should be performed to replace the

prosthesis. The surgery was divided in two stages (two-stage procedures). The first stage involved joint lavage surgery, dead tissue excision and implant removal. Once the debridement had been completed, the cement with antibiotic beads was inserted into the joint cavity to ensure the complete clearance of infection before going to the second stage. During the first stage, the patient was monitored closely for infection, such as symptoms, the culture from periprosthetic tissue, blood samples and other laboratory tests. The pus culture was performed using hemoculture bottles, which might have been unsuitable as the thickness of the pus could impede proper mixing with the culture medium, limiting the growth of infectious agents. However, pus obtained from knee aspiration is often more fluid due to its mixture with synovial fluid. This is similar to using hemoculture bottles for culturing bacteria from ascites fluid[14], pleural fluid[15] or joint fluid.[15] Hemoculture bottles for ascites fluid or joint fluid yielded a better identification rate of causative agents than the standard culture bottle. Similar results were obtained in a study to detect bacteria in pleural fluid in the UK, where the hemoculture bottle method increased the pathogen identification rate by 20.8% compared with sterile culture bottles. [15]

The medical record showed that the medical team followed the patient for one year until ensuring the first stage procedure results before proceeding to the second stage. However, one problem was found in the second stage, namely, soft tissue coverage. The medical team conducted the surgery using the medial gastrocnemius muscle and split-thickness skin grafts.

The treatment of patients with prosthetic infections remains a delicate and difficult decision. While various recommendations exist to shape a diagnosis and make treatment guidelines, many factors remain that the medical team must discuss with patients. The standard treatment guidelines may be inappropriate for the patient's living context at those times. Therefore, when the treatment method must be adjusted to accommodate the needs of patients, it may have to accept that the following side effects could occur. As the example from this patient, the subject developed recurrent infection four months after the second stage procedure. The results of the physical and laboratory examination confirmed the prosthesis infection. Consequently, the patient had repeated surgery to remove the prosthesis, lavage the joint, excise dead tissue and insert the cement with antibiotic beads into the joint cavity a second time.

This report aims to highlight the limitations of the treatment among patients with an infected prosthesis, especially ones undergoing arthroplasty after the bone sarcoma has been removed. In this case, the difference from the typical prosthetic patients involved more than cutting and destroying the surrounding tissues. Because of the oncological outcome, the remaining minimal natural tissue became easily infected, and once the infection had occurred, it could be more sensitive to re-infection. Zajonz and colleagues [9] reported that although treatment was performed according to the recommendations of the Tsukayama classification[11] applied to this group of patients, the limitation of salvage procedures induced the incidence of re-infection as high as 36 to 43%. In addition, the treatment may often significantly affect patients' functional outcomes, even though some patients may require amputation. This study also emphasized that when it became necessary to repeat surgery for prosthesis after an infection, carefully considering both the medical team and the patient was essential. Subjects in the group of multi-morbid patients with previous joint infections Especially need to be highly and carefully monitored.

Conclusion

The infection of the acquired prosthetic joint following bone sarcoma removal surgery remains a common complication and constitutes the primary cause of revision surgery in this patient group. Specific classifications and treatment recommendations for this infection have yet to be established; only guidelines were applied from the treatment recommendations for common knee joint infection. However, context differences and treatment limitations

between the common knee joint infection and acquired prosthetic joint contribute to the high probability of re-infection. In addition, the tissue damage from the surgical procedure of sarcoma removal also leads to repeated surgeries and eventually affects the efficacy of functional outcomes of patients. This present report would like to highlight the limitations of treatment decisions for this group of patients and the complications following that treatment. Thus, caregivers should be careful and decisive in treating this condition from the beginning of infection prevention, which may prove the best way to improve the patient's quality of life.

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IMPACT OF THE COVID-19 PANDEMIC ON FRAGILITY HIP FRACTURE MANAGEMENT AND MORTALITY RATE

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Abstract

Background: The COVID-19 pandemic has greatly affected patients without COVID, including osteoporotic hip fractures. Treatment protocols and time for surgery have been disrupted and delayed resulting in unsatisfactory outcomes. This study compared the mortality rate among patients with osteoporotic hip fractures during the COVID-19 pandemic and during the prepandemic periods.

Methods: The patients' information recorded in the Fracture Liaison Service (FLS) registry was retrospectively reviewed. We defined the prepandemic group as the admissions between May 2019 and March 2020 and the pandemic group as admissions from April 2020 to February 2021. The demographic data were collected, including serum calcium and 25(OH)D levels. Time to surgery, postoperative complications, length of stay and death were obtained and compared between the two periods.

Results: We included 813 patients, with 444 and 369 patients in the prepandemic and the pandemic groups, respectively. Mean age, sex and comorbidities were comparable in both groups. The proportion of patients with insufficient and deficient vitamin D was significantly higher in the pandemic group (46.41 vs. 62.85%, $p<0.01$). Time to surgery and length of hospital stay was significantly longer in the pandemic period ($p<0.05$). The mortality was higher but did not significantly differ in the pandemic period with an adjusted hazard ratio of 1.08 (95% CI = 0.76-1.54).

Conclusion: Properly managing hip fractures during the pandemic is crucial to prevent and reduce morbidity and mortality. Inadequate serum vitamin D level has been noted in the pandemic group but was not associated with mortality rate.

Keywords: COVID-19, Fragility hip fracture, Osteoporotic fracture, Mortality

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Introduction

Osteoporotic fractures are characterized as fractures occurring at a site associated with low BMD, in which incidence increases after the age of 50 years old. [1] Osteoporotic fracture is more common among females. According to a study conducted in the USA, 17.5% of women and 6% of men experience fragility hip fractures throughout their lifetime. [2] Notably, the world will become an aging society shortly; osteoporosis and osteoporotic fractures are unavoidable Patients with osteoporotic fractures have considerably high morbidity and mortality (up to 20% for one-year mortality).[3] The most effective method to reduce mortality and morbidity are early surgery and standard care using a multidisciplinary team approach.[4, 5]

Coronavirus disease 2019 (COVID-19) is caused by a new coronavirus called SARS-CoV-2. COVID-19 is highly contagious and causes severe acute respiratory syndrome with serious morbidity and mortality. WHO announced the COVID-19 pandemic on March 11th, 2020. [6] Since then, each country has established its social distancing guidelines mainly focusing on the restrictions of outdoor activities. Not only do such restrictions affect people's daily activities, but they also have a vast impact on the health service systems. In most hospitals, medical resources and personnel were allocated and shifted toward COVID-19 management. Thus, treating other diseases and injuries, such as fragility hip fractures, was unavoidably delayed and might have resulted in unfavorable outcomes. It resulted in a small number of patients with hip fractures but a higher mortality rate. [7]

The primary objective of this study was to compare the mortality rate among patients with osteoporotic hip fractures during the COVID-19 pandemic and the prepandemic period. Our secondary objective was to determine the impact of the COVID-19 pandemic on patients' characteristics, such as; serum 25OH D level. Furthermore, we aimed to assess the osteoporotic hip fracture treatment outcomes, including the length of hospital stay and other postoperative complications.

Methods

Population

After obtaining approval from the Institutional Review Boards, the retrospective cohort study was conducted in a single tertiary trauma center. Patients with osteoporotic hip fractures during May 2019 and February 2021 were identified. Patients younger than 60 years or those who failed to adhere to the follow-up plan were excluded from the study. Other exclusion criteria were pathologic fractures, secondary osteoporosis and patients with COVID-19. According to the Thai government's social distancing policy established in April 2020, the prepandemic group was defined as those admitted between May 2019 and March 2020. The pandemic group included admissions from April 2020 to February 2021.

All information was collected from the electronic medical records from admission to one-year follow-up period. In addition, demographic data including age, sex, serum calcium, serum 25-OH vitamin D level, patient's comorbidities, fracture types, time from arrival to surgery and type of treatment were retrieved from the Fracture Liaison Service (FLS) registry program. The primary outcome was mortality rate. Other outcome measurements were the length of hospital stay and postoperative complications.

Pre-operative, surgical procedure and postoperative protocol

Patients presenting osteoporotic hip fractures from low energy trauma would be registered in the FLS registry program. If required, internal medicine or interdepartmental consultation was achieved for optimal status for surgery. Surgery was planned as soon as possible after all pre-operative processes were completed. After admission, venous thromboembolism (VTE)

risk was assessed and proper VTE prophylaxis was provided. The difference in preoperative processes between the prepandemic and pandemic periods was the screening laboratory for COVID-19, mostly showing little consequence at time to surgery.

Treatment protocol for cases that could not receive surgery consisted of immobilization with skin traction, which could be transferred to home traction. After the pain subsided, the rehabilitation program for progressive ambulation would be started promptly. Operative treatment remained the gold standard for osteoporotic hip fractures. Determining the types of operations and the types of implants/prostheses depended on the location of the fractures. Closed reduction and internal fixation with cephalomedullary nailing or dynamic hip screws were the mainstays of treatment for intertrochanteric fractures of the femur. On the contrary, the treatment of femoral neck fractures ranged from closed reduction and internal fixation with multiple screws or dynamic hip screws to joint replacement therapy. A patient's age, comorbidity, and activity levels were considered to indicate the most appropriate treatment for each patient.

The postoperative protocol covered progressive ambulation training and gentle range of motion exercises starting the first postoperation day after the pain subsided. In the fixation case, weight bearing was delayed until the bone was united. In contrast with arthroplasty, immediate weight bearing as tolerated was allowed. Patients were often discharged on the third day postoperative when no early complication was detected. A follow-up plan was arranged for two weeks, one month, three months, six months and yearly afterward. Mostly, osteoporotic treatments were initiated and adjusted at the outpatient clinic.

Statistical analysis

Continuous variables such as age, time from admission to surgery, length of hospital stay, serum vitamin D and serum calcium were presented as either mean and standard deviation or median and interquartile ranges (IQR). Categorical variables were demonstrated as frequency and percentage. The differences between continuous data were evaluated using a simple linear regression model or the Wilcoxon rank sum test. Moreover, the chi-square test assessed the differences between categorical variables. Mortality rates between the prepandemic and pandemic periods were compared using survival analysis with the Cox regression model and reported as incidence rate, hazard ratio (HR), adjusted HR and Kaplan-Meier survival curve. Age group, Charlson comorbidity index and early surgery were used to adjust HR due to meaningful clinical signs and associated with mortality rate. Vitamin D status and urinary tract infections were also used to adjust HR due to statistically significant baseline characteristics. Statistical significance was defined as a p-value <0.05. All statistical analyses were performed using STATA, Version 15.0 (College Station, TX, USA: StataCorp LLC.)

Results

This study included patients with osteoporotic hip fractures between May 2019 and February 2021. No patient in this study had positive SARS-CoV-2 during hospitalization. The demographic data are described in **Table 1**, with a total number of 813 patients; the prepandemic period had a slightly higher number of 444 patients while the pandemic consisted of 369. In addition, the mean age of patients in the prepandemic group was somewhat older compared with the pandemic group. The highest prevalence of comorbidities was seen in hypertension, followed by type II diabetes mellitus with no significant difference between the prepandemic and pandemic groups regarding all factors.

The proportion of patients undergoing operative treatment was similar in prepandemic and pandemic intervals. The mean time from admission to surgery was 7.04 days in the

pre-pandemic season, which was substantially delayed in the pandemic season (8.07 days) with statistical significance (p<0.01). Concerning time-to-surgery, the difference was 24.85 hours longer in the pandemic period (95% CI = 6.97 to 42.74). Achieving early surgery was found in 7.23% of patients during the prepandemic period and declined to 3.77% during the pandemic, but without statistical significance. Complications were also noted, and the number of patients with urinary tract infections significantly subsided during the prepandemic. Other postoperative complications did not differ in both groups. The median total hospital length of stay in the prepandemic period was shorter (11 days), orresponding to the pandemic period (12 days) with statistical significance (p= 0.02).

Table 1. Demographic data of enrolled participants

Factors	Pre-COVID-19 pandemic (N=444)	COVID-19 pandemic (N=369)	*p*-value
Sex, n (%)			
- Male	96 (21.62%)	91 (24.66%)	0.31
- Female	348 (78.38%)	278 (75.34%)	
Age, mean (SD)	80.08 (8.34)	79.87 (8.39)	0.72
Age group, n (%)			
- <80 years old	185 (41.67%)	155 (42.01%)	0.92
- ≥80 years old	259 (58.33%)	214 (57.99%)	
Comorbidity, n (%)			
- HT	267 (60.14%)	242 (65.58%)	0.11
- DM	126 (28.38%)	108 (29.27%)	0.78
- DLP	102 (22.97%)	95 (25.75%)	0.36
- CKD	61 (13.74%)	48 (13.01%)	0.76
- Heart disease	43 (9.68%)	49 (13.28%)	0.11
- Asthma/COPD	36 (8.11%)	21 (5.69%)	0.18
- Stroke	56 (12.61%)	43 (11.65%)	0.68
Charlson comorbidity index, n (%)			
- 1 - 3	88 (19.82%)	86 (23.31%)	0.17
- 4 – 6	317 (71.40%)	241 (65.31%)	
- ≥7	39 (8.78%)	42 (11.38%)	
Diagnosis, n (%)			
- Extracapsular	279 (62.84%)	252 (68.29%)	0.10
- Intracapsular	165 (37.16%)	117 (31.71%)	
Treatment, n (%)			
- Conservative	126 (28.38%)	104 (28.18%)	0.95
- Surgery	318 (71.62%)	265 (71.82%)	
Surgery, n (%)			
- Fixation	201 (63.21%)	180 (67.92%)	0.23
- Arthroplasty	117 (36.79%)	85 (32.08%)	

Table 1. Demographic data of enrolled participants (Cont.)

Factors	Pre-COVID-19 pandemic (N=444)	COVID-19 pandemic (N=369)	*p*-value
Type of surgery, n (%)			
- Dynamic hip screw	15 (4.72%)	11 (4.15%)	
- Cephalomedullary nail	188 (59.12%)	167 (63.02%)	
- Multiple screws fixation	5 (1.57%)	2 (0.75%)	
- Hemiarthroplasty	54 (16.98%)	69 (26.04%)	
- Total hip arthroplasty	56 (17.61%)	16 (6.04%)	
Time from admission to surgery (day), mean (SD)	7.04 (4.15)	8.07 (5.01)	0.01*
Early surgery (within 48 hr), n (%)	23 (7.23%)	10 (3.77%)	0.07
Complications, n (%)			
- Pressure sore	22 (4.95%)	9 (2.44%)	0.06
- UTI	51 (11.49%)	63 (17.07%)	0.02*
- Pneumonia	39 (8.78%)	29 (7.86%)	0.64
- DVT	3 (0.68%)	3 (0.81%)	0.82
- PE	12 (2.70%)	10 (2.71%)	0.99
- Delirium	57 (12.84%)	44 (11.92%)	0.69
- Wound infection	4 (0.90%)	2 (0.54%)	0.55
LOS (day), median (IQR)	11 (8, 15)	12 (8, 17)	0.02*

HT = Essential hypertension, DM = Type II diabetes mellitus, DLP = Dyslipidemia CKD = Chronic kidney disease, COPD = Chronic obstructive pulmonary disease, UTI = Urinary tract infection, DVT = Deep vein thrombosis, PE = Pulmonary embolism

The mean serum 25(OH)D level of patients in the prepandemic group was 31.99 ng/ml and 28.19 ng/ml in the pandemic group ($p<0.01$). The vitamin D level was 3.80 ng/ml lower in the pandemic group (95% CI =1.98-5.61). Most patients in the prepandemic group had sufficient vitamin D (53.59%). During the pandemic, the number of patients with sufficient vitamin D levels declined and the number of those with insufficient vitamin D rose remarkably (26.79 and 38.83%, respectively, $p<0.01$) (**Table 2**). The mean serum calcium level was similar among both groups (9.29 and 9.23 mg/dl, respectively).

The Kaplan-Meier survival curve in **Figure 1** shows the overall mortality rate and one-year mortality rate, i.e., 21.17% in the prepandemic and 24.93% in the pandemic groups. The results showed that the COVID-19 pandemic period exhibited a slightly increased patient mortality rate but failed to reach statistical significance (HR 1.14, 95% CI=0.90-1.45) (**Table 3**). The serum 25(OH)D insufficient and deficient levels also did not significantly affect the mortality rate (1.12, 95% CI = 0.86-1.46 and 1.03, 95% CI = 0.76 to 1.40, respectively).

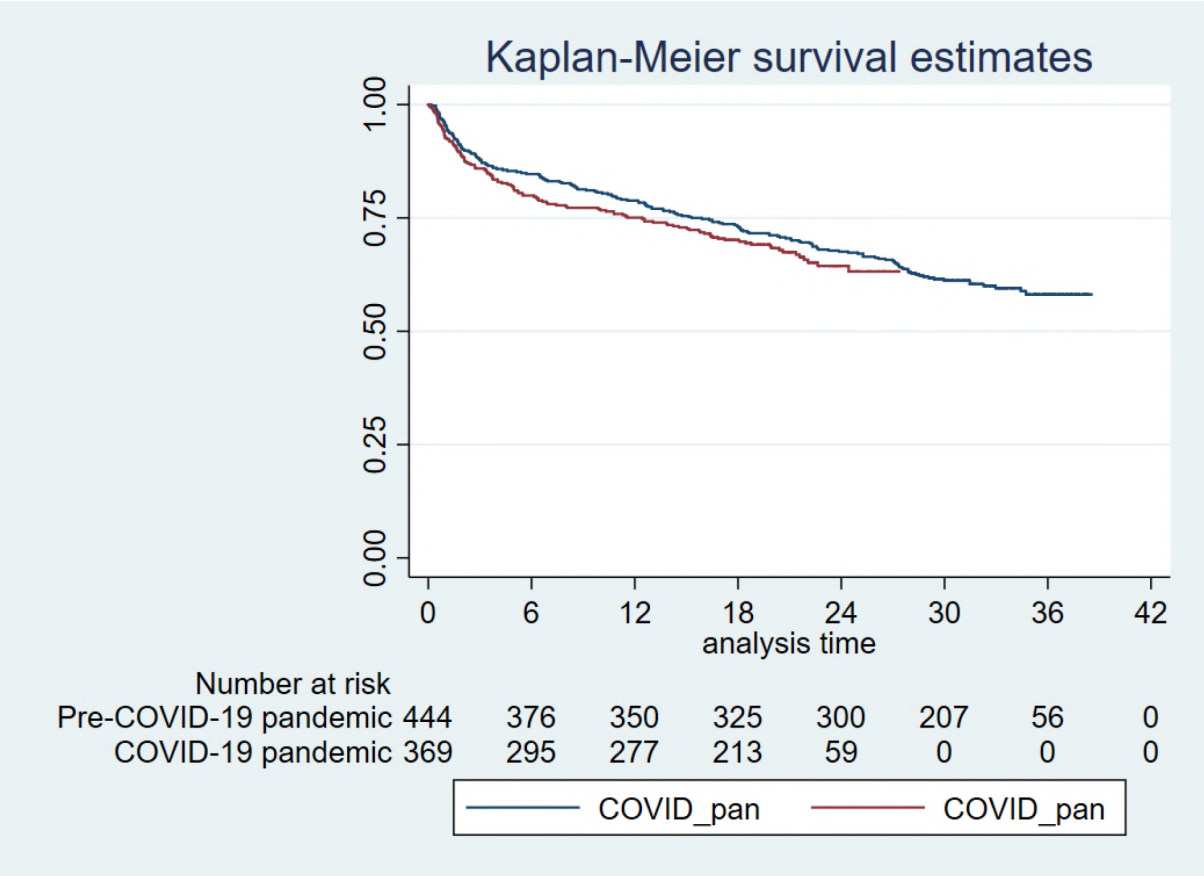

Figure 1. Kaplan-Meier survival curve

Table 2. Serum 25(OH)D and serum calcium level between prepandemic and pandemic groups

	Pre-COVID-19 pandemic (N = 418)	**COVID-19 pandemic (N= 358)**	***p*-value**
Serum 25(OH)D level, mean (SD)	31.99 (13.83)	28.19 (11.59)	<0.01*
Vitamin D status, n (%)			
- Sufficiency	224 (53.59%)	133 (37.15%)	
- Insufficiency	112 (26.79%)	139 (38.83%)	<0.01*
- Deficiency	82 (19.62%)	86 (24.02%)	
Serum calcium, mean (SD)	9.29 (0.46)	9.23 (0.69)	0.12

Discussion

Our study compared the baseline characteristics and treatment outcomes between COVID-19 prepandemic and pandemic periods. Our primary outcome was the mortality rate, as illustrated in **Figure 1**. The prepandemic period one-year mortality rate was 21.17% compared with 24.93% during the pandemic. Compared with the study in our hospital before the FLS Program was adopted, the one-year mortality rate of patients with osteoporotic hip fractures was 29.33%.[8] Shiga et al. revealed that an operative delay of more than 48 hours from the time of admission increased the odds of 30-day mortality by 41% and of one-year mortality by 32%.[9] Due to limitations during the COVID pandemic, the percentage of patients receiving early surgery within 48 hours was only 3.77% compared with 7.23% in the prepandemic period. This limitation could be one of the factors accounting for

Table 3. Effect of COVID-19 and Vitamin D status on mortality rate

	N	Dead	Person Months	Incidence rate	HR (95%CI)	Adjusted HR (95%CI)
COVID-19 status						
- Pre-COVID-19	444	177	10,884.93	0.016	Ref.	Ref.
pandemic	369	123	6,132.90	0.020	1.14 (0.90-1.45)	1.08 (0.76-1.54)**
- COVID-19 pandemic						
Vitamin D status						
- Sufficiency	357	130	7,785.77	0.017	Ref.	Ref.
- Insufficiency	251	97	5,081.87	0.019	1.12 (0.86-1.46)	1.19 (0.82-1.72)***
- Deficiency	168	59	3,344.73	0.018	1.03 (0.76-1.40)	0.98 (0.64-1.50) ***

**Adjusted for Age group, Charlson comorbidity index, Early surgery, Vitamin D status, and UTI

*** Adjusted for Age group, Charlson comorbidity index, Early surgery, COVID-19 pandemic status and UTI

the higher mortality rate compared with other studies. Nevertheless, after all the concerned variables were analyzed, the mortality rate did not show statistical significance between the two groups (adjusted HR=1.08, 95% CI = 0.76 to 1.54).

The demographic data of fragility hip fractures during the outbreak of COVID-19 have been reviewed in many different countries. They all agreed that the mean patients' age was significantly older than that in the nonpandemic group, and the proportion of low energy injuries was notably higher during the pandemic.[10-12] While other studies demonstrated a decrease in total visits to the trauma department and the number of high energy injuries during the lockdown, Nunez et al. revealed the number of osteoporotic hip fractures admitted in the hospital had no significant differences between each period.[13] In contrast, our study demonstrated that the number of patients with osteoporotic hip fractures slightly decreased during the pandemic. The nature of the Asian family could explain this. During the lockdown, younger people tended to spend more time at home. The elderly were taken better care of by their offspring, decreasing their risk of falling. In our study, patients' comorbidity differed slightly between the two periods but failed to reach statistical significance. Age and comorbidities were adopted to determine the Charlson comorbidity index to predict the ten-year mortality of patients. We also considered it a parameter to assess the patient's overall health. In this study, we stratified the Charlson comorbidity index in three subgroups, the score 1 to 3, 4 to 6, and over 6. Most patients fell in the second group with a score of 4 to 6 for prepandemic and pandemic periods. The result correlated to findings from Anusitviwat et al. that the Charlson comorbidity index did not significantly differ in both groups. They also explained that this parameter did not statistically affect the inhospital complications among patients with fragility hip fractures. [14] According to Jarvis et al., during the COVID-19 period, young patients tended to move faster from arrival to surgery because elective surgical cases were postponed and the operating rooms were reserved for urgent and emergency cases.[15] This was not true for geriatric patients who needed more time for assessment and pre-operative management before surgery. During the COVID-19 pandemic, due to the hospital's policy on healthcare professional allocation and other reasons, the number of operative theaters was reduced. Elective operations were suspended because human and nonhuman medical resources were

reserved for urgent and emergency cases. Hip fractures were prioritized as urgent cases with a high morbidity and mortality rate. The hospital's pre-operative policy for surgery was altered during the COVID-19 pandemic. In addition to the standard protocols, every patient with a fever or upper respiratory tract symptoms during admission would have requested a new PCR test for SARS-CoV-2 for safety reasons. The surgical procedure would have been postponed until the test showed a negative result, taking at least 8 hours. The surgery was usually preceded by the next day. Moreover, for patients indicating evidence of close contact with patients positive for COVID-19-positive, the surgery must be delayed until the PCR test on the 7th day showed a negative result. Even though we prioritized osteoporotic hip fracture as an urgent case, the pre-operative surgery process during the pandemic still took longer than usual. In our study, the surgery was delayed for approximately 24.89 hours during the pandemic. Our findings were parallel to Narang et al., who reported the increased proportion of patients with hip fractures experiencing a delay in operation during the pandemic period in the UK.[16] Another finding in our study was further extended hospital stays during the pandemic period. The estimated length of hospital stay in the prepandemic period was 11 days versus 12 days during the pandemic (p=0.02). Because surgery was delayed, complications such as urinary tract infections occurred at higher incidences (p=0.02), the hospital stay was subsequently extended.

In agreement with the US Endocrine Society, vitamin D status was defined as sufficiency, insufficiency and deficiency. The sufficiency level was defined as >30-100 ng/mL or >75-200 mol/L, while the insufficiency level was 20 to 30 ng/mL and the deficiency level was <20 ng/mL. Inadequate vitamin D levels accounted for secondary osteoporosis and were found to be related to an increased risk of falling, resulting in fractures.[17-19] During the prepandemic period, most patients had sufficient vitamin D levels (53.59%), while in the pandemic period, the percentage of sufficiency subsided to 37.15% with statistical significance (p<0.01). Most patients in the pandemic group established an insufficiency level (38.83%). Mean serum 25(OH) D level declined by 3.80 ng/mL (95% CI=1.98-5.61).We believe that the social distancing policy hindered people from outdoor activities, involving vitamin D production. Another possible cause was the disruption of healthcare services and medications for noncommunicable chronic diseases, including vitamin D supplements. It has been reported in many countries worldwide that the COVID-19 pandemic vastly affected the overall health system in need of medical personnel and resource allocations. Following the Joint Position Statement on managing patients with osteoporosis, it was presumed that patients had stopped treatment and delayed diagnostic study due to social distancing protocol.[20] Similarly, the National Health Service of England and other studies demonstrated a decrease in outpatient attendance and the use of FRAX and DXA scans during the lockdown.[21-23] Vitamin D deficiency is associated with an increased risk of hip fractures, as reported in related studies.[18] Maintaining a normal serum 25(OH) D level is essential, and this remains challenging for all of us on behalf of healthcare providers. Telemedicine was proposed to keep contact with patients and reduce the interruption of pharmacologic treatment for patients having missed their appointment.[24, 25] Reorganizing the anti-osteoporotic therapy based on the convenient method of administration and duration of action was generally recommended.[26, 27] We adopted this service due to our circumstances, for osteoporosis and especially postfracture follow-ups, to make our patients strictly adhere to osteoporotic medications and supplements. The patients were assessed for their general health conditions by phone calls from the medical staff and their medications would be later sent by mail. We emphasized that chronic diseases should not be understated or dismissed during the pandemic.

This study constitutes the first to compare the one-year mortality rate of nonCOVID patients with osteoporotic hip fractures between the prepandemic and the pandemic periods. Even though our study contained the most prominent study population conducted in a single trauma center in Thailand, several limitations were encountered. Firstly, some information was missing based on the nature of the retrospective study research. Thirty-seven patients did not have the result of serum 25(OH)D level at admission, 26 patients (5.86%) in the prepandemic, and 11 patients (2.98%) in the pandemic group. The analyses of vitamin D and calcium status (**Table 2**) were performed after excluding those 37 patients. Secondly, this study did not address the functional outcomes of both nonoperative and operative treatments, which the COVID-19 pandemic would influence. Additionally, the results may only be generalized for some regions due to the different management policies for nonCOVID diseases. We advocate further multicenter studies in the future.

In the future, if a further COVID-19 pandemic occurs again and because most of the population is vaccinated, we can use only rapid tests to screen for COVID-19 instead of RT-PCR. This will decrease waiting time for surgery and cause early ambulation among patients.

Conclusion

During the COVID-19 pandemic, the number and characteristics of patients with fragility hip fractures remained similar to those in the prepandemic period. Time to surgery was significantly delayed due to the allocation of medical personnel and limited medical resources. The overall mortality rate and one-year mortality rate increased during the pandemic but failed to reach statistical significance. The proportion of patients with insufficient and deficient vitamin D increased significantly. Osteoporosis treatment should be continued to prevent fractures and decrease mortality.

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COMPARISON OF EFFICACY IN RENOPROTECTION BETWEEN AZILSARTAN AND ENALAPRIL: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) are reported to improve renal outcomes among patients with hypertension and chronic kidney disease (CKD), but there might be substantial differences in their renoprotective effects. Azilsartan medoxomil is a relatively new available ARB, highly specific angiotensin type 1 receptor and superior in terms of blood pressure reduction, with respect to other ARBs.

Methods: The study employed a randomized controlled trial; hypertensive subjects with albuminuria >30 mg/g creatinine at the outpatient clinic, Phramongkutklao Hospital, Bangkok, Thailand were randomly assigned to azilsartan 40-80 mg/day (n=27) or enalapril 10-40 mg/day (n=23) for 24 weeks. The primary outcome was the change in urine albumin creatinine ratio (UACR). UACR, estimated glomerular filtration rate (GFR), blood pressure and serum electrolytes were evaluated at baseline, 12 and 24 weeks.

Results: A total of 50 patients with hypertension and albuminuria were recruited. At the end of treatment, systolic blood pressure level was significantly reduced in the azilsartan group compared with the enalapril group (-12.2 mmHg [95%CI -18.9 to -5.5] vs. -1.1 mmHg [95% -7.8 to 5.7], p=0.021). In addition, at 24 weeks, significantly reduced median UACR was observed in the azilsartan group compared with that of the enalapril group (-59.9 mg/g Cr [95% CI -284.6 to -31.0] vs. -40.4 mg/gCr [95% CI -129.4 to 88.3], p=0.026)). No statistically significant difference was found between the two groups in hyperkalemia, estimated GFR, acute kidney injury and serious adverse events.

Conclusion: This study demonstrated that azilsartan had superior antihypertensive and albuminuric efficacy compared with the standard dose of enalapril without increasing adverse events.

Keywords: Hypertension, Antihypertensive therapy, Azilsartan Medoxomil, Enalapril, Microalbuminuria, Macroalbuminuria, Renoprotective effect

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Introduction

Activation of the renin-angiotensin-aldosterone system (RAAS) promotes systemic hypertension with kidney disease and excessive angiotensin II leading to intraglomerular hypertension, salt retention and profibrotic, inflammatory activation of fibrogenic mediators causing long term adverse effects to the kidneys.[1, 2] RAAS inhibitors including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are first-line antihypertensives to slow chronic kidney disease (CKD) progression.[3] Clinical studies indicated that novel ARBs especially azilsartan medoxomil has a tighter and longer-lasting binding to the angiotensin II subtype-1 (AT1) receptor than other ACEIs or ARBs, leading to more effectively reduced blood pressure. [4, 5] An observational study demonstrated that a blood pressure target of <140/90 mmHg was achieved by a significantly greater proportion of patients in the azilsartan treatment than that of the ACEIs treatment.[6] An initial trial also showed that azilsartan had significantly greater reduced proteinuria than other ARBs among patients with CKD.[7]

Azilsartan medoxomil more selectively inhibits angiotensin II-induced activation of AT1 receptors. Its affinity is greater than 10,000-fold for AT1 receptors than for AT2 receptors.[8] Azilsartan medoxomil at its maximal dose has more benefit on blood pressure control over olmesartan and valsartan at their maximal, approved doses without increasing adverse events.[9] Moreover, azilsartan demonstrated antihypertensive effects with improved vascular endothelial function and lower albuminuria along with reduced tubular cast formation and glomerular injury in an animal model.[10] However, limited studies have been conducted regarding the effects of azilsartan on urine albumin among patients with hypertension. This study aimed to compare efficacy regarding renoprotective effect between azilsartan medoxomil and enalapril, which is commonly used and available worldwide.

Methods

Study population

This constituted an open-label, randomized controlled study conducted among patients with hypertension and albuminuria, Phramongkutklao Hospital, Bangkok, Thailand. This study was reviewed and approved by the Royal Thai Army Medical Department Institutional Review Board. Written informed consent was obtained from the participants following the WMA Declaration of Helsinki Ethics principles for medical research involving human subjects (approval number: R221h/60). The study was registered in the Thai Clinical Trials Registry and obliged to disclose details of the 24 mandatory items of the WHO International Clinical Trials Registry Platform (Trial identification number was TCTR20220426002, First submitted date: 22/04/2022). Treatment protocol patients were selected using a method of block randomization by a research pharmacist. Randomization was performed using a central computerized randomization program.

From April 2018 to May 2019, patients attending the outpatient clinic in medicine were recruited and screened for eligibility. All eligible patients were required to be over 18 years of age and have essential hypertension with albuminuria more than 30 mg/day for more than three months, stable systolic blood pressure of 140 to 160 mmHg in more than three screening visits or to be taking antihypertensive medication other than ACEIs/ARBs without adjusting glucose lowering medications or lipid lowering agents within three months. No treatment was given with RAAS inhibitors within three months before starting the study. Exclusion criteria included hyperkalemia, secondary or malignant hypertension, chronic alcohol consumption, known hypersensitivity to ARBs or ACEIs, pregnancy, kidney transplantation and end stage kidney disease (ESKD). All patients were required to provide written informed consent before the initiating any study-related procedures.

Intervention

During the 24-week treatment period, all patients in each group received the assigned study drug once daily after breakfast. Patients in the azilsartan group received a dosage of 40 mg daily for the first 8 weeks and then 80 mg daily for the subsequent 16 weeks. Patients in the

enalapril group received a dosage of 20 mg daily for the first 8 weeks and then 40 mg daily for the subsequent 16 weeks to control blood pressure less than 130/80 mmHg. Both treatments were given for 24 weeks. A complete medical history and physical examination were performed on all subjects. Adherence was monitored by pill counting during each visit. Once a patient was given the assigned medication, the use of other anti-hypertensive medications was prohibited.

All patients were scheduled for first followed-up visits at four weeks in the run-in period. After the run-in period, patients were scheduled to follow-up at 8, 12 and 24 weeks. Adjusting the medications to reach the systolic blood pressure target was based on office blood pressure measurements (Omron HBP-9020 Kentaro Automatic sphygmomanometer blood pressure monitor AC 100V, Japan).

At the time of recruitment, baseline characteristics were collected by physician's face-to-face visits using a questionnaire. At each follow-up visit, the office blood pressure and heart rate were measured and information was gathered regarding concomitant medication use and adverse events. Measurement of the office blood pressure was performed three times at one-to two-minute intervals by the patients themselves with recommendation from trained physicians. Patients were required to rest for at least five minutes in a seated position, without consuming alcohol or caffeine, exercising or smoking at least 30 minutes before recording blood pressure. The laboratory tests including blood urea nitrogen, serum creatinine, calculation of estimated glomerular infiltration rate using the 2009 Chronic Kidney Disease Epidemiology Collaboration Equation, serum potassium level and urine albumin creatinine ratio (UACR) were measured at baseline and during treatment at weeks 12 and 24. Thirty milliliters of fresh urine were centrifuged at 4,000 rpm for 10 minutes. UACR were measured using immunonephelometric assay method.

The primary outcome was the change of urinary albumin level after 24 weeks in the azilsartan group, compared with that of the enalapril group. The following secondary outcomes were prespecified: change of estimated glomerular filtation rate (GFR) and blood pressure.

Statistical analysis

The sample size was determined on the basis of the results of a related study provided to detect a 20% lower albuminuria in the ARBs group than in the ACEIs group (11). A sample-size of 22 subjects per group was required to verify the statistical difference between azilsartan and enalapril with at least a 90% power and a two-sided type I error α of 5%. Accordingly, the number of subjects evaluable for the primary endpoint was determined to be 50 in total. All analyses were based on the intention-to-treat approach.

Normal data distribution was confirmed using the Kolmogorov-Smirnov test. Differences between groups were comparing using Chi-square test or Fischer's exact test for categorical data. For the primary efficacy endpoint, summary statistics and two-sided 95% confidence intervals (CI) of the mean ± standard deviation (SD) or medians with interquartile range (IQR) values were determined and Student's t test or Mann-Whitney U test was performed. Within group changes were evaluated using paired t-tests. All statistical analyses were performed using SPSS Inc., Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

Results

A total of 80 patients provided informed consent to participate in the trial, of whom 50 were randomized, 23 patients in the enalapril group and 27 patients in the azilsartan group (**Figure 1**). The baseline characteristics were similar between the two groups (**Table 1**). The mean age and estimated GFR was 69.5± 10.4 years and 60.8±23.4 mL/min/1.73 m^2, respectively. Comorbid illnesses included dyslipidemia (84%), type 2 diabetes mellitus (80%), CKD stages 3 to 4 (56%) and cardiovascular disease (16%). Mean systolic and diastolic blood pressure was 142.2±13.1 and 75.3±10.2 mmHg, respectively. The medications prescribed before this study to all patients in both groups did not differ significantly. During study in the treatment

group, the average dose of enalapril was 34 mg/day and average dose of azilsartan was 70 mg/day. Treatment compliance was 90% in the enalapril group and 100% in the azilsartan group.

Changes in renal function and albuminuria over period of the study

Estimated GFR, biochemical profiles and UACR are shown in **Table 2.** During the follow-up period of 24 weeks, median UACR decreased from baseline in the azilsartan -treated group at 12 weeks (-59.3 (95%CI -376.8 to -24.8), $p<0.05$) and 24 weeks (-59.9 (95%CI -284.6 to -31.0), $p<0.05$), whereas they did not significantly change in the enalapril group. These changes significantly differed between the two groups (**Figure 2**). No difference was found between the two groups regarding estimated GFR and serum potassium at baseline or the end of study.

Changes in blood pressure during the study

Blood pressure during the study is shown in **Table 3.** Comparing between groups, the azilsartan-treated group exhibited a greater decrease in systolic blood pressure than that in the enalapril-treated group (12.2 (95% CI= -18.87 to -5.53) vs. -1.05 (95%CI= -7.76 to 5.65) mmHg, $p=0.021$) at 24 weeks whereas change of diastolic blood presssure at 24 weeks did not significantly differ between the two groups (-6.65 (-15.85, 2.55) vs. -8.64 (-14.54, -2.74) mmHg, $p=0.696$).

Safety profile

During the 24-week study, the drugs were equally well-tolerated and no differences were observed in the incidence of treatment-emergent adverse events including acute kidney injury, cardiac arrhythmia and hyperkalemia between the two treatment groups (**Table 4**). Overall incidence of hypotension-related events was comparable to the two drugs: 2 of 23 patients (8.6%) in the enalapril group compared with 3 of 27 patients (11.1%) in the azilsartan group. Two patients in the enalapril group developed chronic cough.

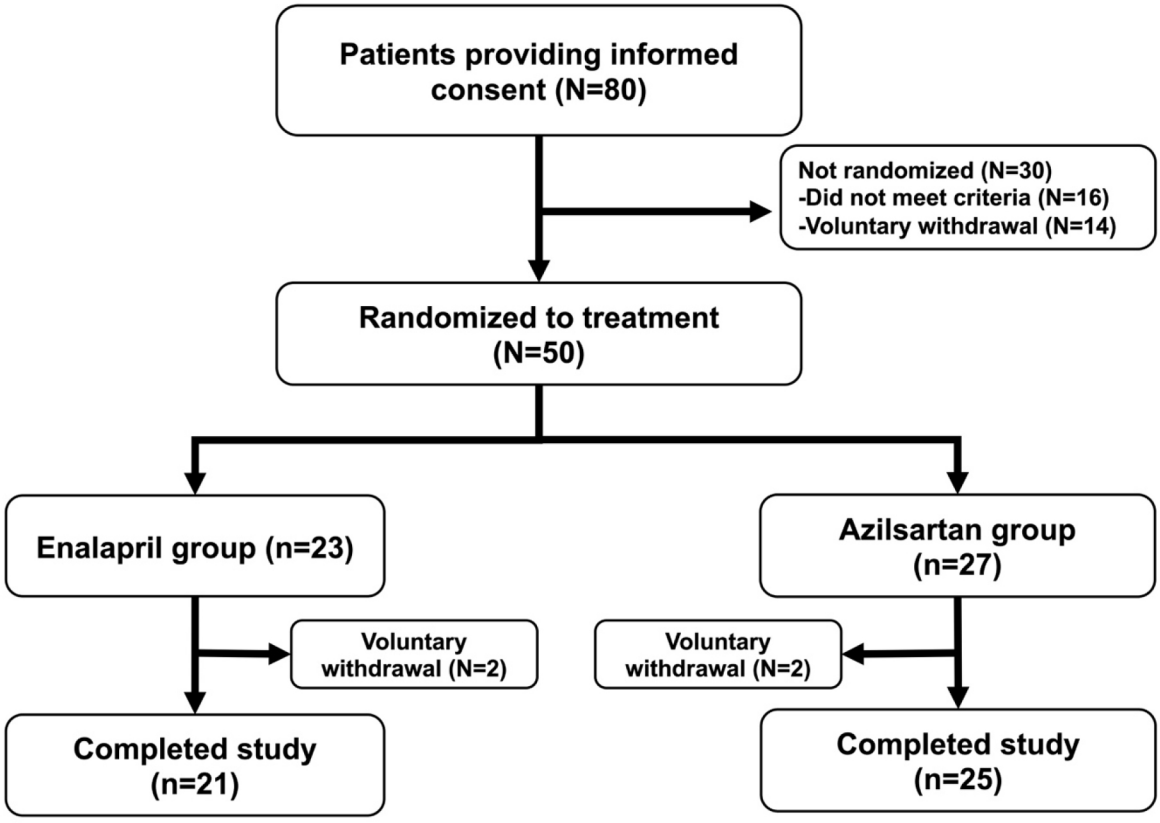

Figure 1. Flow chart of enrolled patients

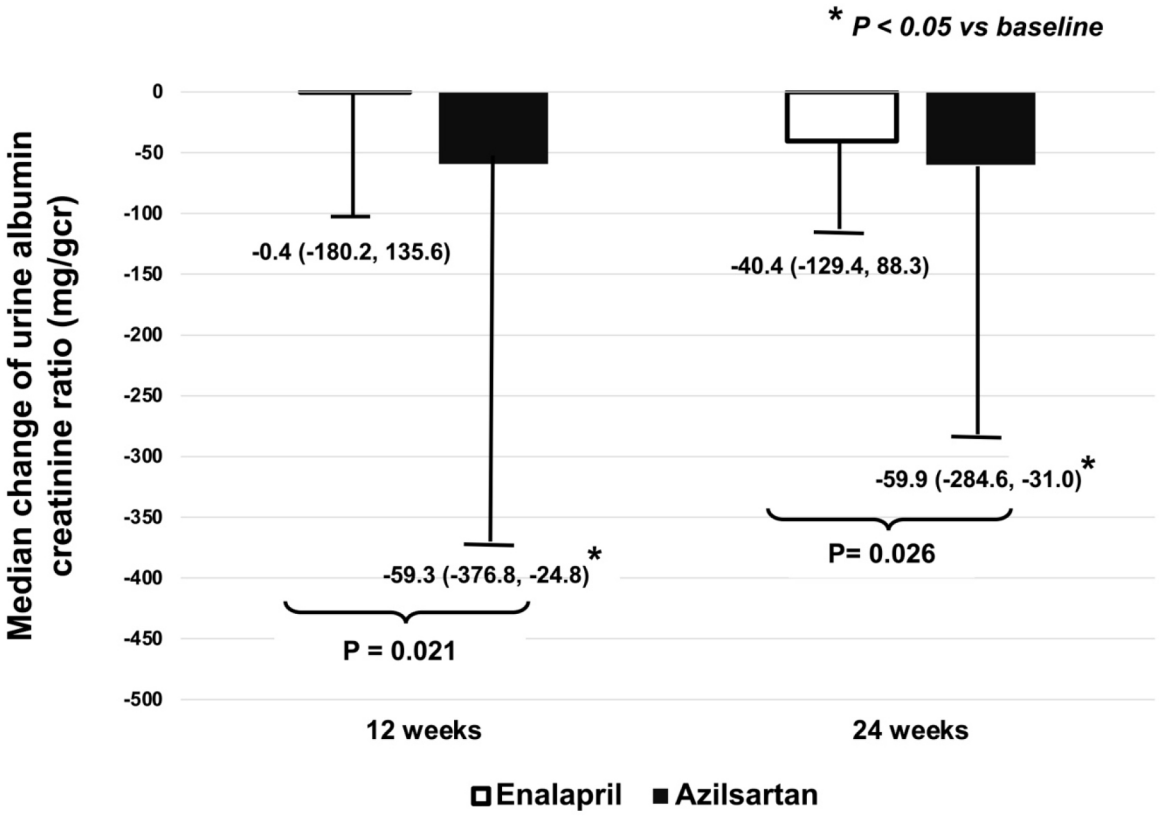

Figure 2. Urine albumin creatinine ratios in the enalapril group (open bar) and azilsartan group (closed bar)

Table 1. Baseline characteristics of the study population

Variables	Enalapril (N=23)	Azilsartan (N=27)
Male (N, %)	8 (34.8%)	13 (48.1%)
Age (years)	70.0±9.3	68.3±12.3
Body weight (kg)	61.4±10.9	66.2±12.9
Systolic blood pressure (mmHg)	143.3±12.1	141.8±14.0
Diastolic blood pressure (mmHg)	74.7±9.2	75.7±12.8
Estimated glomerular filtration (mL/min/1.73 m^2)	60.35 ± 24.11	61.15 ± 25.04
Urine albumin creatinine ratio (mg/gCr)	165.3 (76.3, 581.5)	154.8 (72.2, 1000)
Serum potassium (mEq/L)	4.54 ± 0.53	4.32 ± 0.37
Co-morbid diseases (N, %)		
- Type 2 diabetes	18 (78.2%)	22 (81.5%)
- Dyslipidemia	19 (82.6%)	23 (85.2%)
- Cardiovascular disease	5 (21.7%)	3 (11.1%)

Table 1. Baseline characteristics of the study population (Cont.)

Variables	Enalapril (N=23)	Azilsartan (N=27)
Previous medications (N, %)		
- Calcium channel blockers	17 (73.9%)	19 (70.4%)
- Beta-blockers	9 (39.1%)	7 (25.9%)
- Diuretics	7 (30.4%)	8 (29.6%)

Data are mean ± SD and median with interquartile range

Table 2. Comparison of the changes of renal function, serum potassium and albuminuria before and after treatment between two groups

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Median urine albumin creatinine ratio (mg/gCr)			
Baseline	165.3 (76.3, 581.5)	154.8 (72.2, 1000)	0.876
Week 12	186.9 (62.9, 385.5)	85.2 (31.1, 565.8)	0.224
Change from baseline with 95% CI at week 12	-0.4 (-180.2, 135.6)	-59.3 (-376.8, -24.8)*	0.021
Week 24	120.7 (38.6, 236.2)	65 (26.6, 98.7)	0.197
Change from baseline with 95% CI at week 24	-40.4 (-129.4, 88.3)	-59.9 (-284.6, -31.0)*	0.026
Mean estimated glomerular filtration rate (mL/min/1.73 m^2)			
Baseline	60.4±24.1	61.2±25.0	0.909
Week 12	63.9±22.2	60.7±27.0	0.679
Change from baseline with 95% CI at week 12	-0.7 (-4.32, 2.91)	-0.41 (-4.54, 3.72)	0.917
Week 24	62.9±23.6	55.7±27.4	0.360
Change from baseline with 95% CI at week 24	-1.62 (-6.76, 3.52)	-3.12 (-7.21, 0.97)	0.632
Mean serum potassium (mEq/L)			
Baseline	4.5±0.5	4.3±0.4	0.102
Week 12	4.5±0.4	4.5±0.4	0.991
Change from baseline with 95% CI at week 12	-0.01 (-0.25, 0.24)	0.16 (-0.01, 0.32)	0.232
Week 24	4.4±0.4	4.5±0.4	0.439
Change from baseline with 95% CI at week 24	-0.11 (-0.34, 0.13)	0.13 (-0.03, 0.29)	0.080

Data are mean ± SD and median with interquartile range (IQR); Weeks 12 and 24 value compared with baseline; $^*p<0.05$

Table 3. Comparison of the changes of blood pressure before and after treatment between two groups

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Mean systolic blood pressure (mmHg)			
Baseline	143.3±12.1	141.8±14.04	0.692
Week 12	136.8±17.4	132.9±10.5	0.376

Table 3. Comparison of the changes of blood pressure before and after treatment between two groups (Cont.)

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Change from baseline with 95% CI at week 12	-5.35 (-12.91, 2.21)	-8.96 (-14.31, -3.62)*	0.409
Week 24	141.6±13.2	128.9±10.8	0.001
Change from baseline with 95% CI at week 24	-1.05 (-7.76, 5.65)	12.2 (-18.87, -5.53)*	0.021
Mean diastolic blood pressure (mmHg)			
Baseline	74.7±9.2	75.7±12.8	0.745
Week 12	76.0±13.1	72.2±9.8	0.263
Change from baseline with 95% CI at week 12	0.8 (-5.25, 6.85)	-3.48 (-8.24, 1.27)	0.248
Week 24	68.8±19.2	67.9±9.8	0.844
Change from baseline with 95% CI at week 24	-6.65 (-15.85, 2.55)	-8.64 (-14.54, -2.74)*	0.696

Data are mean ± SD and mean± 95%CI. Week 12 and 24 value compared with baseline; $^{*}p<0.05$

Table 4. Adverse events during the study

	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Acute kidney injury	1 (4.3%)	0 (0%)	0.460
Hyperkalemia	5 (21.7%)	3 (11.1%)	0.444
Cough	2 (8.6%)	0 (0%)	0.207
Cardiac arrhythmia	0	0	NA
Hypotension-related events	2 (8.6%)	3 (11.1%)	0.815

Discussion

The results indicated that treatment with azilsartan for 24 weeks significantly augmented improved albuminuria among patients with CKD and that this effect occurred by a mechanism dependent on reducing blood pressure. However, renal function did not significantly differ between groups. This study provided evidence of potent blood pressure and albuminuria lowering effects with azilsartan among patients with CKD.

Azilsartan is a new ARB exhibiting a higher affinity and selectively on AT1 receptors than other ARBs(12) and azilsartan provides significantly more effectiveness in lowering blood pressure than other ARBs.[9, 13, 14] Similarly, in a double-blind, controlled, randomized trial, patients with hypertension, treated with azilsartan medoxomil indicated significantly more effectiveness than ramipril in lowering clinic systolic blood pressure and better tolerance.[5] Our results supported that azilsartan (40 to 80 mg once daily) provided a significantly greater reduction from baseline of clinic-measured systolic blood pressure than enlalapril (20 to 40 mg once daily) among patients with albuminuria and hypertension at week 24 after the treatment period. The results from our study demonstrated that azilsartan was significantly superior to enlalapril in reducing clinic systolic blood pressure with high rate of treatment compliance in the both groups (90% in the enalapril group and 100% in the azilsartan group).

Among antihypertensive agents, both ACEIs and ARBs demonstrated a renoprotective effect attributable to both antihypertensive and antiproteinuric effects. The positive effect of azil-

sartan on albuminuria in this study was consistent with a related study, showing that inhibition of angiotensin II action improved albuminuria and inhibited an intrarenal renin-angiotensin system activity marker among patients with uncontrolled hypertension.[15] Limited studies have directly compared the renoprotective effects, including protection against kidney injury and albuminuria of ARBs and ACEIs among patients with hypertension. One study demonstrated that telmisartan and enalapril significantly reduced proteinuria, urinary liver-type fatty acid-binding protein (L-FABP) and urinary endothelin-1 levels, but telmisartan appeared to be more potent than enalapril in protecting against kidney injury among patients with CKD.[16] Recently, another study reported that azilsartan treatment significantly decreased proteinuria and blood pressure compared with candesartan among patients with CKD.[7] This was consistent to our study; azilsartan reduced albuminuria compared with enalapril during 24 weeks of treatment. In addition, the severity of albuminuria correlated with blood pressure levels and responded to lowering blood pressure.[17] Therefore, significantly reduced albuminuria induced by azilsartan might be related to reduced systolic blood pressure. Finally, the albuminuric effects of azilsartan may be related to strong RAAS inhibition to AT1 receptors with long and strong antihypertensive effects in a clinical setting.

In the meta-analysis of randomized controlled trials comparing ACEIs or ARBs with placebo among patients with diabetes and albuminuria, ARBs reduced risks of ESKD, but ACEIs failed to reduce risks of ESKD.[18] Based on the renoprotective effects, ARBs may be preferred for diabetic patients with albuminuria. Our findings support the notion that azilsartan 40 to 80 mg/day had potent antihypertensive and albuminuria effects by blocking the inhibitory effect of angiotensin II on kidney damage by reducing renal oxidative stress and inflammation.[19] Further, ESKD risk showed a clear dependence on albuminuria and blood pressure reduction.[20] Therefore, the RAAS blockers regimen require a dual strategy, targeting both systolic blood pressure and albuminuria reduction. The potent and long acting of antihypertensive efficacy of azilsartan did not increase risk of adverse events, as the two groups were equally well tolerated in the study. A slightly higher incidence was observed of postural dizziness with azilsartan and candesartan (11.1 vs. 8.6%). However, these events were generally of mild intensity and resolved without intervention.

Several limitations were encountered in the present study. First, the long term outcomes of ARBs treatment concerning patients with CKD were not demonstrated in this study, making these agents undesirable for long term renoprotective effects. Second, a significant decrease in systolic blood pressure was observed in the azilsartan-treated group. The significantly reduced albuminuria from azilsartan might be related to tight blood pressure control. Finally, the present study was a -single center trial and the results might not be generalizable to patients with hypertensive patients and all CKD stages. Moreover, the sample size of this study was small and the trial was underpowered to demonstrate an effect.

In conclusion, this study demonstrated improved systolic blood pressure and albuminuria after a short course of azilsartan treatment among patients with hypertension compared with enalapril without severe adverse events. Thus, azilsartan could be useful for treating patients with hypertension for their antihypertensive capacity and for their albuminuric actions.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PT and BS designed the study, reviewed the manuscript and shared first authorship. BS and NN acquired most of the data and drafted

the manuscript. PT, OS and NN confirmed the authenticity of all the raw data, analyzed the data and revised the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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DIAGNOSTIC VALUE OF MEDIAN NERVE CONDUCTION VELOCITY ACROSS WRIST AMONG PATIENTS WITH SUSPECTED CARPAL TUNNEL SYNDROME

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Abstract

Background: Carpal Tunnel Syndrome (CTS) is the most prevalent type of compressive neuropathy. At present, electrodiagnosis is considered the gold standard in diagnosing CTS. However, no clear cutoff point has been established regarding the diagnostic value of the median nerve conduction velocity, across the carpal tunnel area, among patients with CTS.

Objectives: This study aimed to determine the cutoff point for patients' median nerve conduction velocity (NCV), to diagnose CTS among suspected patients, which is determined using electrical stimulations conducted across the carpal tunnel area. The present study also aimed to determine the diagnostic value of the median nerve conduction velocity across the carpal tunnel area, compared with the standard method.

Methods: This cross-sectional study was conducted among 56 participants (106 wrists) suspected of CTS. Motor and sensory NCV across the carpal tunnel was investigated to yield diagnostic value of CTS compared with the standard technique.

Results: The optimal cutoff point in diagnosing CTS using the wrist to midpalm conduction velocity, was $\leq$ 40 m/s (with a sensitivity of 87.04% and specificity of 87.18%) for the sensory nerve conduction study, and $\leq$ 35 m/s (with a sensitivity of 88.06% and specificity of 89.74%) for the motor nerve conduction study.

Conclusion: Our study determined that the optimal cutoff conduction velocities for CTS diagnosis, using the wrist-to-midpalm electrical stimulation method, was $\leq$40 m/s for the sensory nerve, and $\leq$35 m/s for the motor nerve.

Keywords: Carpal tunnel syndrome, Median nerve, Nerve conduction velocity
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Introduction

The median nerve compression causes Carpal Tunnel Syndrome (CTS) as it passes through the carpal tunnel and constitutes the most prevalent type of focal nerve entrapment among patients. To elaborate, CTS causes pain, numbness and tingling in the hands and affects the patient's daily functioning.[1-3]

Given the negative effects of CTS, accurate and efficient diagnosis is important for research and clinical practice, and in turn, patient recovery. The Nerve Conduction Study (NCS) method has been considered the gold standard for diagnosing CTS. [4]

In the current standard method, electrical stimulation is applied at the wrist and the elbow.[5-7] However, a major problem with this kind of application is the slowing of conduction between the wrist and the elbow, possibly caused by other abnormalities proximal to the level of the wrist.[8] Losing large fast-conducting myelinated nerve fibers could also result in slower nerve conduction velocity and delayed distal latency. Therefore, prolongation of the distal latency does not suggest focal demyelination. [9]

In this study, we used segmental measurements of velocity across the lesion, which is helpful in distinguishing CTS from other forms of peripheral neuropathy. [1, 10-11] Our method has the advantage of showing the exact site of the lesion.[12] Despite its advantages, the method we suggested is not yet considered the standard practice; segmental motor conduction studies such as wrist to mid-palm nerve conduction velocity are still considered an optional technique by the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM).[6, 13] Thus, a clear cutoff point has yet to be established regarding the diagnostic value of the median nerve conduction velocity, across the carpal tunnel area among patients with CTS.

Therefore, the primary aim of this research was to determine the cutoff point for patients' median nerve velocity, to accurately diagnose possible patients with CTS, determined using electrical stimulations conducted across the carpal tunnel area. In addition to the cutoff point, the present study aimed to find the diagnostic value of the median nerve conduction velocity across the carpal tunnel area, compared with the standard method.

Methods

This cross-sectional study was conducted among 56 outpatients (106 wrists) at the Department of Rehabilitation Medicine, Phramongkutklao Hospital. The study's protocol was approved by the Institutional Review Board, the Royal Thai Army Department (IRBRTA 1348/2562). All participants consented to participate in the study. The data were collected between December 2019 and August 2020. Eligibility criteria included Thai adults 18 years or older displaying one or more of the following primary symptoms in median nerve distribution: numbness, pain or tingling. We excluded participants who had (1) received treatment by local corticosteroid injection or surgical release for CTS before enrollment, (2) other neurologic diseases such as polyneuropathy, cervical radiculopathy or other neuropathy of the upper extremities and (3) anatomical anastomosis such as Martin Gruber anastomosis and Riche–Cannieu anastomosis.

Demographic data of all participants were collected. A single physiatrist, with over ten years' experience, managed the wrist-to-mid palm nerve conduction study among all participants. On the same day, all participants received the standard nerve conduction study to diagnose CTS, carried out by a physiatrist with at least two years' experience in NCS and supervised by an experienced physiatrist. The methods of both practices are elaborated below.

Wrist to mid-palm nerve conduction velocity study

All participants received palmar stimulation. Midpalm stimulation for the sensory nerve was stimulated between the 2nd and 3rd metacarpal

bones and recorded from the 2nd digit. The motor nerve was recorded from the abductor pollicis brevis muscle. The stimulation site was at the proximal thenar crest with the cathode pointed to the abductor pollicis brevis muscle.[4, 14] The electromyographer moved the stimulation probe finely to elicit the maximum potential (**Figure 1).** Distances were gauged using a tape measure from cathode to cathode. Motor and sensory nerve conduction velocity was calculated by dividing the distance between stimulation sites (wrist and midpalm) by the latency difference. An electromyographer with ten years' experience in EDx stimulated the midpalm in all cases.

Routine nerve conduction study

Confirmation of CTS was achieved in the routine NCS study including (1) median motor study recording the abductor pollicis brevis, stimulating the wrist and antecubital fossa; (2) ulnar motor study recording abductor digiti minimi, stimulating the wrist and elbow; (3) median sensory response, recording digit 2 or 3, stimulating the wrist and (4) ulnar sensory response, recording digit 5, stimulating the wrist. (8) Additionally, bilateral studies were conducted. The results were classified in four groups; normal, mild, moderate and severe, based on the following recommendation of Stevens.[15]

Mild: prolonged distal sensory latency ± SNAP amplitude below the lower limit of normal

Moderate: abnormal median sensory latency as above and prolonged median motor distal latency

Severe: Prolonged median motor and sensory distal latencies, with either an absent SNAP or low amplitude or absent thenar CMAP

When median studies were equivocal, sensory indexes were combined to maximize sensitivity to detect CTS.

Based on the AANEM reference value[6]; prolonged distal median sensory more than 4.0 m/s., prolonged distal median motor latency more than 4.5 m/s., decreased onset-to-peak SNAP amplitude of median sensory nerve potential below 11 μV and decreased CMAP amplitude of the median motor nerve potential below 4.1 mV, all considered as abnormal.

Statistical Analysis

A Receiver Operating Characteristic (ROC) curve was plotted to compare the standard NCS results and the wrist-to-midpalm stimulation technique to determine the optimal cutoff point of median nerve conduction velocity across

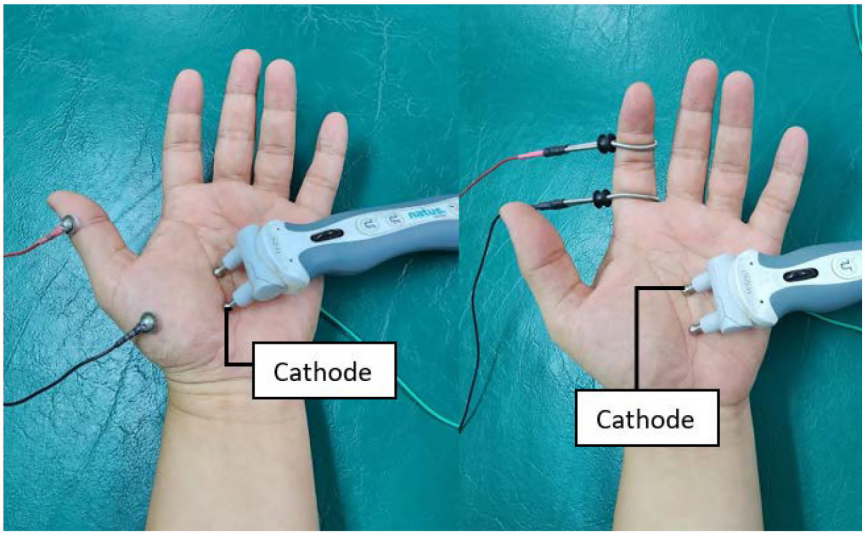

Figure 1. Midpalm stimulation site; left for motor and right for sensory stimulation. Electromyographer will move the probe to determine the highest amplitude. Distances are measured from cathode to cathode.

the wrist among patients with CTS. Then the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio(+LR) and negative likelihood ratio(-LR) were calculated. Statistical analyses were performed using STATA, Version 13.0.

Results

We assessed 56 participants (112 wrists) with suspected CTS for eligibility and then excluded 6 wrists due to their history of steroid injection and wrist surgery. Thus, we calculated our results from 56 participants (106 wrists). Participants included 47 females and 9 males, with a mean age of 54.11±11.44 years, as shown in **Table 1.** Of the 56 participants, the majority were right hand dominant (91%). The 106 wrists included in the analysis were classified as follows: 40 (37.74%) were documented as normal, 16 (15.09%) as mild, 37 (34.90%) as moderate and 13 (12.26%) as severe CTS. The mean (±SD) median nerve conduction velocity across the carpal tunnel in wrists with and without CTS is summarized in **Table 2**.

Table 1. Demographic data of enrolled participants

	N (56)
Age	54.1±11.4
Height (cm)	158.2±8.0
BMI	24.4±3.8
Sex	
female	47 (83.9)
Duration of symptoms(month)(106 hands)	9.9±10.4

Displayed as mean±SD and number (percent)

Table 2. Values of median nerve conduction velocity (mean±SD) across the carpal tunnel in wrists with and without CTS, categorized by severity of the CTS.

	Normal (m/s) N=40 wrists	Mild (m/s) N=16 wrists	Moderate (m/s) N=37 wrists	Severe (m/s) N=13 wrists
Sensory NCV	48.56±7.79	38.09±5.43	29.01±7.55	No response
Motor NCV	45.12±12.63	34.74.5±6.57	24.77±7.56	15.09±5.78

Median sensory nerve conduction velocity

The mean (±SD) median sensory nerve conduction velocity across the carpal tunnel was 48.56±7.79 m/s in wrists without and 31.61±8.09 m/s in wrists with CTS, with means of 38.09±5.43 m/s in mild and 29.01±7.55 m/s in moderate CTS. The sensory nerve action potential was absent in severe CTS.

Median motor nerve conduction velocity

The mean (±SD) of median motor nerve conduction velocity across the carpal tunnel was 45.12±12.63 m/s in wrists without and 24.98±9.50 m/s in wrists with CTS, with a mean of 34.74.5±6.57 m/s in mild, 24.77±7.56 m/s in moderate and 15.09±5.78 m/s in severe CTS.

The ROC curves to determine the cutoff points were also drawn. Compared with the current standard method, our study determined

that the optimal cutoff point in diagnosing CTS, using the wrist-to-midpalm conduction velocity method, was ≤40 m/s (with a sensitivity of 87.04% and specificity of 87.18%) for the sensory nerve, and ≤35 m/s (with a sensitivity of 88.06% and specificity of 89.74%) for the motor nerve. The area under the ROC curve was 0.939 (95% CI, 0.0869-0.978) for the sensory nerve (**Fig. 2** left) and 0.912 (95%CI, 0.841 to 0.958) for the motor nerve (**Figure 2** right). Notably; however, a lower nerve conduction velocity value would be more effective in ruling in CTS. Similarly, a higher value would also hold excellent power to rule out CTS, as shown in **Table 3**.

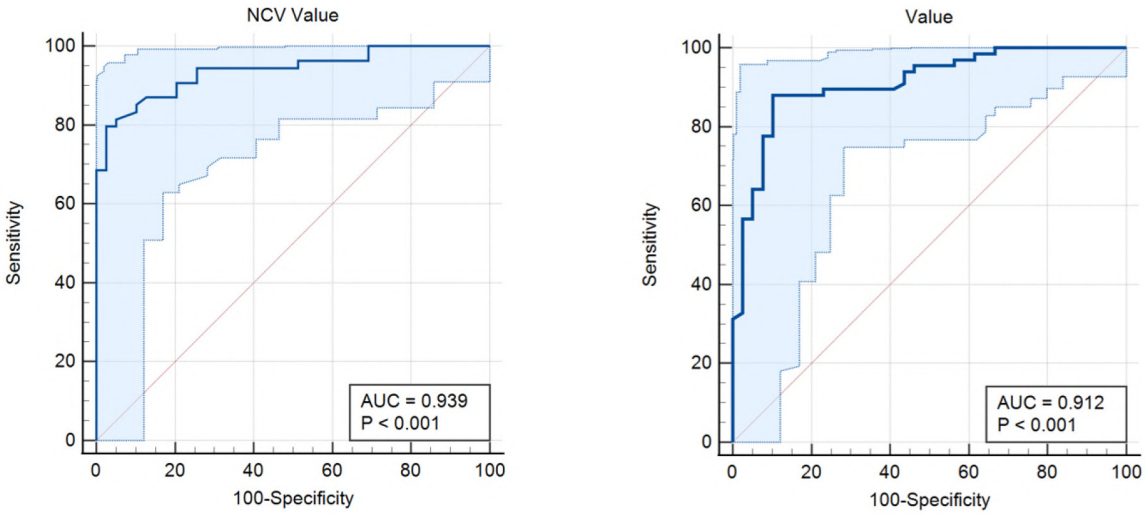

Figure 2. Receiver operator characteristic (ROC) curves with area under the curve of nerve conduction velocity across the carpal tunnel area, to diagnose CTS among patients; left for sensory NCV and right for motor NCV.

Table 3. Diagnostic properties of each different cutoff value

	NCV for cutoff points (m/s)	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV	+ LR	- LR
Sensory N=93 hands	≤ 37.25	81.48(68.6-90.7)	94.87(82.7-99.4)	95.7	78.7		
	≤ 38.78	85.19(72.9-93.4)	89.74(75.8-97.1)	92.0	81.4		
	≤ 40.00	87.04(75.1-94.6)	87.18(72.6-95.7)	90.4	82.9	5.29	0.12
	≤ 41.84	90.74(79.7-96.9)	79.49(63.5-90.7)	86.0	86.4		
	≤ 42.74	94.44(84.6-98.8)	74.36(57.9-87.0)	83.6	90.6		
Motor N=106 hands	≤ 27.78	64.18(51.5-75.5)	94.87(82.7-99.4)	95.6	60.7		
	≤ 31.50	77.61(65.8-86.9)	92.31(79.1-98.4)	94.5	70.6		
	≤ 35.00	88.06(77.8-94.7)	89.74(75.8-97.1)	93.7	81.4	5.03	0.08
	≤ 37.20	89.55(79.7-95.7)	76.92(60.7-88.9)	87.0	81.1		
	≤ 40.00	91.04(81.5-96.6)	56.41(39.6-72.2)	78.2	78.6		

NCV, nerve conduction velocity; PPV, positive predictive value; NPV, negative predictive value.; +LR, positive likelihood ratio; -LR, negative likelihood ratio.

Discussion

According to the AANEM, the reference value for median motor nerve conduction velocity among adults is 49 m/s at a-ll ages.[6] However, a strong relationship between conduction velocity and nerve fiber diameter has been reported in the literature. Recent studies have documented that the diameter of the peripheral motor nerve gradually decreases until it reaches the target muscle.[16] The mentioned reference value might be inaccurate in the distal segment.

The present research studied, for the first time, the optimal cutoff point of the wrist to midpalm median nerve conduction velocity in diagnosing CTS. The results of this study indicated that the optimal cutoff point was ≤40 m/s (with a sensitivity of 87.04% and specificity of 87.18%) for the sensory nerve and ≤35 m/s (with a sensitivity of 88.06% and specificity of 89.74%) for the motor nerve. These values can be useful in diagnosing CTS because no clear cutoff point of this technique has been studied until now.

Our results revealed that the mean (±SD) median nerve conduction velocity across the carpal tunnel was 45.12±12.63 m/s among normal subjects for the motor nerve and 48.56±7.79 m/s for the sensory nerve. Our results were similar to a related study by Jun Kimura[4] reporting that the motor and sensory nerve conduction velocity was slow when less than 41 m/s and 44 m/s, respectively, in the wrist-to-palm segment.

Additionally, our results suggested a tendency existed for decreasing values of the mean (±SD) median nerve conduction velocity across the carpal tunnel area with increasing severities of CTS among patients, as shown in **Table 1**. These findings may be used to determine the cutoff values in future studies, to more clearly define the categories of patients with CTS by severity.

This study encountered limitations. Firstly, although NCS has been considered the gold standard, no universally accepted reference standard has been established to diagnose CTS.[17] Secondly, skin temperature was not monitored during the study. However, all participants were warmed with a hydrocollator pack before NCS testing. Variations in hand temperature could affect the results of nerve conduction velocity; thus, future studies should control this factor. [18] Next, height significantly correlated to nerve conduction velocity. [19] Therefore, these values may be invalid among patients who are taller and shorter than average individuals. In addition, our reference values might not be generalized to the advanced age group. Finally, this method was the surface measurement which couldn't reflect the actual nerve length.

Unfortunately, the midpalm conduction velocities yielded sensitivity and specificity between 87 and 89% compared with the standard procedure. It couldn't replace the standard NCS. Considering the positive likelihood ratio of motor and sensory nerve conduction velocities at 35m/s and 40 m/s, respectively, 5.03 and 5.29 indicated a moderate effect for CTS diagnosis, given a positive result, respectively. However, the negative likelihood ratio was 0.08 for motor and 0.12 for sensory nerve conduction velocity. These values indicated a moderate to strong effect to exclude CTS when the result was negative. Thus, we recommend using sensory and motor NCV across the wrist as screening tools.

Conclusion

This study determined that the optimal cutoff point to diagnose CTS, using the wrist-to-midpalm electrical stimulation method, was ≤40 m/s for the sensory nerve and ≤35 m/s for the motor nerve.

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TRENDS IN THE PREVALENCE OF TYPE 2 DIABETES AMONG ROYAL THAI ARMY PERSONNEL AND ASSOCIATED FACTORS FROM 2017 TO 2021

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Abstract

Background: Diabetes is one of the essential noncommunicable diseases associated with an increased risk of atherosclerosis and cardiovascular diseases. However, limited information is available regarding type 2 diabetes (T2D) among Royal Thai Army (RTA) personnel.

Objectives: The present study aimed to determine the prevalence of T2D among RTA personnel and its associated factors.

Methods: We carried out a serial cross-sectional study from 2017 to 2021. A total of 235,491 active-duty RTA personnel aged 35–60 years were included in the study. We defined T2D as fasting plasma glucose ≥126 mg/dL or having a history of T2D diagnosed by medical personnel, or having a history of taking antihyperglycemic medication. We used a multivariable logistic regression model to estimate adjusted prevalence ratios (APR) and 95% confidence intervals (CIs) for behavioral factors associated with T2D.

Results: Age- and sex-adjusted T2D prevalence among RTA personnel was 17.9% (95% CI 17.5%-18.2% in 2017 and then decreased to 16.5% (95% CI 16.1%–16.8%) in 2021 (p for trend < 0.001). The age-adjusted prevalence of T2D among males and females was 17.6 (95% CI 17.4%–17.8%) and 11.3 (95% CI 11.0%–11.7%), respectively. The independent behavioral factors associated with T2D included current cigarette smoking (APR 1.12; 95%CI 1.10-1.14), current alcohol use (APR 1.03; 95%CI 1.01-1.05), regular exercise (APR 0.89; 95%CI 0.87-0.90), body mass index ≥30 kg/m^2 (APR 2.21; 95%CI 2.15-2.27) and hypertension comorbidity (APR 3.97; 95%CI 3.88-4.05).

Conclusion: Our study indicated that T2D is a common health issue, especially among males, higher-aged participants and RTA personnel residing in Bangkok and the northeast. Cigarette smoking, alcohol use, and sedentary behavior played an essential role in the prevalence of T2D in this population. Furthermore, obesity and HT comorbidity were related to T2D.

Keywords: Diabetes, Hypertension, Body Mass Index, Prevalence, Associated factors

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Introduction

The World Health Organization indicated that noncommunicable diseases (NCDs) are estimated to account for 70% of the 57 million deaths worldwide, and one third of those comprise cardiovascular diseases.[1] Similarly, 74% of all deaths in Thailand were caused by NCDs and one fourth by cardiovascular diseases. [1] Diabetes, characterized by T2D, is one of the essential NCDs, a common health problem independently associated with an increased risk of atherosclerosis cardiovascular diseases (ASCVD).[2-6]

Diabetes is one of the most significant global health problems and exhibits a rising trend. The International Diabetes Federation (IDF) has estimated the global diabetes prevalence in 2019 to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[1] In Thailand, the National Health Examination Survey (NHES) indicated that the prevalence of diabetes among Thai adults aged 15 years (who received a diagnosis of type 2 diabetes (T2D), had taken antihyperglycemic drugs or have fasting plasma glucose (FPG) 126 mg/dL) increased from 8.9% in 2014 (NHES V)[2] to 9.5% in 2019 (NHES VI).[1] Furthermore, approximately two thirds of Thai patients with T2D had hypertension (HT) as comorbidity[2], increasing the risk for its complications and ASCVD. [4]

Under the Royal Thai Army (RTA) of Thailand, males comprise approximately 90% of personnel aged 20 to 60. A recent study reported that behavioral risk for NCDs among RTA personnel was relatively high compared with that of the general Thai population; for example, obesity, a potential risk factor for T2D among RTA personnel, significantly rose over the rest of five years[4]. However, limited information remains available regarding the T2D situation and its factors associated with RTA personnel. Nationwide, approximately 50,000 RTA personnel aged at least 35 participate in yearly health examinations provided by the RTA Medical Department (RTAMED). The investigators aimed to determine T2D among RTA personnel using the physical health examination database available from 2017 to 2021.

Methods

Study Design and Subjects

RTA personnel's physical health examination database is available from 2017 to 2021. Therefore, to explore the trends in T2D prevalence, we carried out a serial cross-sectional study from 2017 to 2021. The dataset was retrieved from RTA personnel's annual health examination database after obtaining permission from the RTAMED in Bangkok, Thailand. Therefore, the study design and subjects in the present study were explained using established methods from the recent related study of Sakboonyarat et al.[4,5] The RTAMED provides annual health examinations for RTA personnel through the Armed Forces Research Institute of Medical Sciences; the Army Institute of Pathology and Phramongkutklao Hospital located in the Bangkok Metropolitan Area and 36 RTA hospitals nationwide, including ten RTA hospitals in central, ten in northeastern, ten in northern and six in southern Thailand. The data of health examinations were reported to the RTAMED in Bangkok.

The inclusion criteria for this study included active-duty RTA personnel aged 35 to 60 years nationwide. Because we used the collected data, the data for RTA personnel not participating in each annual health examination were excluded from the data for that year. In the present study, we proposed to determine the prevalence of T2D; thus, the RTA personnel not having a record of FPG level in their data were excluded. Finally, 235,491 RTA personnel from 2017 to 2021 were eligible.

Data Collection

A self-report guide was conducted using a standardized case report form for obtaining demographic characteristics and behavioral risk factors, including age, sex, health scheme, smoking status, alcohol use and regular exercise. Moreover, information on comorbidities was also collected including the history of HT and T2D. A history of T2D and a history of HT were defined using the data from the responses to the following questions:[1] "Have you ever received a diagnosed of T2D or taken antihyperglycemic drugs?"

and[2] "Have you ever received a diagnosis of HT or taken antihypertensive drugs?" Behavioral factors were defined using data from the responses to the questionnaire. Current alcohol consumption and smoking were defined as having a history of consuming alcohol and cigarette smoking within 12 months.[6, 7] Regular exercise was defined as exercising 30 min/day and at least three days/week.[8]

The annual health examination dataset also included anthropometric measurements of weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP) and laboratory data including FPG. Blood pressure (BP) was measured using an automatic blood pressure monitor by an operator trained in the standardized technique according to the Thai guidelines on treating HT.[9] We defined T2D as FPG ≥126 mg/dL, having a history of T2D diagnosed by medical personnel or taking antihyperglycemic medication.[10] HT comorbidity was defined by a systolic blood pressure (SBP) ≥140 mmHg, a diastolic blood pressure (DBP) ≥90 mmHg, a history of HT diagnosed by medical personnel or a history of taking antihypertensive medication.[9] Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared: $(kg)/(m)^2$. BMI was classified in five groups according to the Asia-Pacific perspective, including underweight (<18.50 kg/m^2), normal (18.50 to 22.99 kg/m^2), overweight (23.00 to 24.99 kg/m^2), obese I (25.00 to 29.99 kg/m^2) and obese II (≥30.00 kg/m^2).[11]

Statistical Analysis

All statistical analyses were performed using StataCorp. 2021, Stata Statistical Software: Release 17 (College Station, TX: StataCorp LLC). We calculated the frequency distribution of demographic characteristics and behavioral factors to describe the study subjects. Categorical data such as sex, age categories, regions, health schemes, smoking status, alcohol consumption, regular exercise, BMI categories, FPG categories, history of T2D and HT comorbidity were presented as percentages. Continuous variables including age, BMI and FPG were presented as mean and standard deviation (SD). We calculated the prevalence of T2D and presented it as a percentage with a 95% confidence interval (CI). P for trend was calculated using regression to test the statistical significance of trends in the prevalence of T2D from 2017 to 2021. The nonlinear trend was tested first by adding a quadratic term to the regression model. If the result was not significant, a linear trend was tested. We performed a univariable analysis to determine the association between associated factors and the prevalence of T2D. A multivariable logistic regression model was used to determine the factors associated with T2D. The variables that were significant in univariable analysis were recruited in the final model including sex, age, region, scheme, smoking status, alcohol consumption, regular exercise, BMI categories, HT comorbidity and year. After running a logit model, the adjrr (margin) command was used to calculate the adjusted prevalence ratio (APR), which presented a corresponding 95% CI. A two-sided *p*-value less than 0.05 was considered statistically significant.

Ethics Considerations

The study was reviewed and approved by the Institutional Review Board, Royal Thai Army Medical Department (approval number S067h/64 & S056h/65) in compliance with international guidelines including the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP). Due to the use of secondary data, a waiver of documentation of informed consent was employed. The Institutional Review Board, Royal Thai Army Medical Department approved the informed consent waiver.

Results

Characteristics of Participants

Table 1 shows the demographic characteristics of 253,491 RTA personnel from 2017 to 2021. In all, approximately 90% of RTA personnel were males. The mean age of study participants ranged from 46.7 to 48.0 years. Almost two fifths of participants resided in central regions.

The prevalence of current smokers continuously increased from 24.6% in 2017 to 28.4% in 2021. The average FPG of study participants was 103.4±36.0 mg/dL in 2017, then rose to 105.1± 39.5 mg/dL in 2019 and decreased to 102.5±32.7 mg/dl in 2021. Totally, 14.5% of participants reported a history of T2D in 2017 dropping to 12.3% in 2021. In all, approximately 40% of study participants had HT comorbidity.

Table 1. Demographic characteristics of participants from 2017-2021

Year Characteristics	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)
No. of participants	39,899	45,626	51,208	53,004	45,754
Sex					
Male	36257 (90.9)	40567 (88.9)	45845 (89.5)	46559 (87.8)	41270 (90.2)
Female	3642 (9.1)	5059 (11.1)	5363 (10.5)	6445 (12.2)	4484 (9.8)
Age (years)					
mean±SD	48.0±7.1	47.6±7.3	47.4±7.5	47.5±7.7	46.7±7.7
35-39	6781 (17.0)	8551 (18.7)	10338 (20.2)	11378 (21.5)	11517 (25.2)
40-44	7354 (18.4)	9149 (20.1)	9990 (19.5)	9513 (17.9)	8338 (18.2)
45-49	6301 (15.8)	7230 (15.8)	7911 (15.4)	8732 (16.5)	7927 (17.3)
50-54	9947 (24.9)	10022 (22.0)	10453 (20.4)	9582 (18.1)	7562 (16.5)
≥55	9516 (23.9)	10674 (23.4)	12516 (24.4)	13799 (26.0)	10410 (22.8)
Regions					
Bangkok	7320 (18.3)	9949 (21.8)	10906 (21.3)	11139 (21.0)	5552 (12.1)
Central	15220 (38.1)	17423 (38.2)	19159 (37.4)	19760 (37.3)	18358 (40.1)
Northeast	7238 (18.1)	7550 (16.5)	8508 (16.6)	9994 (18.9)	7660 (16.7)
North	7413 (18.6)	5386 (11.8)	7401 (14.5)	6740 (12.7)	8674 (19.0)
South	2708 (6.8)	5318 (11.7)	5234 (10.2)	5371 (10.1)	5510 (12.0)
Scheme					
Civil servant medical benefit	38977 (97.7)	44736 (98.0)	50290 (98.2)	51466 (97.1)	44999 (98.3)
Social Security	576 (1.4)	430 (0.9)	489 (1.0)	1124 (2.1)	646 (1.4)
Universal Coverage	346 (0.9)	460 (1.0)	429 (0.8)	414 (0.8)	109 (0.2)
Smoking status					
Never	22333 (56.7)	26064 (57.9)	27270 (54.7)	25296 (50.1)	23601 (51.7)
Ex-smoker	7322 (18.6)	6865 (15.2)	9324 (18.7)	10597 (21.0)	9099 (19.9)
Current smoker	9720 (24.7)	12122 (26.9)	13295 (26.6)	14645 (29.0)	12966 (28.4)
Alcohol consumption					
Never	10318 (26.3)	12267 (27.3)	12735 (25.0)	10692 (21.2)	11661 (25.5)
Ex-drinker	3850 (9.8)	4421 (9.8)	5479 (10.7)	6069 (12.0)	5415 (11.9)
Current drinker	25132 (63.9)	28303 (62.9)	32780 (64.3)	33771 (66.8)	28565 (62.6)
Regular exercise					
No	16683 (42.6)	18604 (42.3)	18578 (37.3)	23609 (45.1)	20432 (44.8)
Yes	22446 (57.4)	25397 (57.7)	31293 (62.7)	28707 (54.9)	25146 (55.2)
Body mass index (kg/m^2)					
mean±SD	25.1±3.6	25.2±3.7	25.3±3.7	25.3±3.7	25.3±3.8
18.50-22.99	10512 (26.3)	11759 (25.8)	13039 (25.5)	13705 (25.9)	11656 (25.5)
<18.50	657 (1.6)	656 (1.4)	698 (1.4)	725 (1.4)	621 (1.4)
23.00-24.99	10076 (25.3)	11467 (25.1)	12992 (25.4)	13279 (25.1)	11482 (25.1)
25.00-29.99	15071 (37.8)	17358 (38.0)	19355 (37.8)	19835 (37.4)	17037 (37.2)

Table 1. Demographic characteristics of participants from 2017-2021 (Cont.)

Year Characteristics	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)
No. of participants	39,899	45,626	51,208	53,004	45,754
≥30.00	3583 (9.0)	4386 (9.6)	5124 (10.0)	5460 (10.3)	4958 (10.9)
Fasting plasma glucose (mg/dL)					
mean±SD	103.4±36.0	104.0±36.8	105.1±39.5	103.0±33.9	102.5±32.7
<100	26033 (65.2)	29451 (64.5)	32857 (64.2)	34928 (65.9)	30522 (66.7)
100-125	9844 (24.7)	11580 (25.4)	12607 (24.6)	12857 (24.3)	10929 (23.9)
≥126	4022 (10.1)	4595 (10.1)	5744 (11.2)	5219 (9.8)	4303 (9.4)
History of type 2 diabetes					
No	34110 (85.5)	40294 (88.3)	45140 (88.2)	46117 (87.0)	40145 (87.7)
Yes	5789 (14.5)	5332 (11.7)	6068 (11.8)	6887 (13.0)	5609 (12.3)
Hypertension comorbidity					
No	22815 (57.2)	27265 (59.8)	31149 (60.8)	31752 (59.9)	26931 (58.9)
Yes	17084 (42.8)	18361 (40.2)	20059 (39.2)	21252 (40.1)	18823 (41.1)

Prevalence of Type 2 Diabetes among RTA Personnel from 2017 to 2021

Table 2 presents the prevalence of T2D among RTA personnel from 2017 to 2021. Age- and sex-adjusted T2D prevalence among RTA personnel was 17.9% (95% CI 17.5 to 18.2% in 2017 and then decreased to 16.5% (95% CI 16.1 to 16.8%) in 2021 (*p* for trend <0.001) (**Figure 1)**. The age-adjusted prevalence of T2D among males and females was 17.6 (95% CI 17.4 to 17.8%) and 11.3 (95% CI 11.0 to 11.7%), respectively. **Figure 2** shows the prevalence of T2D stratified by age group and sex. Age- and sex-adjusted prevalence of T2D among RTA personnel residing in Bangkok, the north and northeast tended to increase (*p* for trend <0.001).

Factors Associated with Type 2 Diabetes

The APR from the multivariable logistic regression model is shown in **Table 3.** The independent behavioral factors associated with T2D included current cigarette smoking (APR 1.12; 95%CI 1.10 to 1.14), current alcohol use (APR 1.03; 95%CI 1.01 to 1.05), regular exercise (APR 0.89; 95%CI 0.87 to 0.90), body mass index 30 kg/m^2 (APR 2.21; 95%CI 2.15 to 2.27) and hypertension comorbidity (APR 3.97; 95%CI 3.88 to 4.05).

Discussion

This study represented the extensive epidemiologic study of T2D prevalence among RTA personnel in Thailand for over five years. Regarding the NHES VI in 2019, the prevalence of T2D, using a similar definition to the present study, among Thai adults 15 years was 9.5%.[1] Compared with the NHES VI, the overall T2D prevalence among RTA personnel was higher (18.4%); however, the present study included participants aged 35 to 60 years. In addition, this finding may be explained by the difference in the behavioral factors, which were established to be at risk for T2D, including a higher prevalence of history of alcohol consumption (70%) and higher obesity prevalence among RTA personnel compared with the study participants in the NHES VI.[1] On the other hand, we found that decreasing trends in the prevalence of T2D among RTA personnel slightly dropped from 17.9% in 2017 to 16.5% in 2021. Although this trend was statistically significant, extended study participants may have caused it. T2D prevalence in this population remains relatively high. Conversely, the NHES V in 2014[12] and VI in 2019 [1] demonstrated that the overall prevalence of T2D among Thai adults slightly rose from 8.9 to 9.5% over five years.

We found that the prevalence of T2D among male participants was significantly higher than

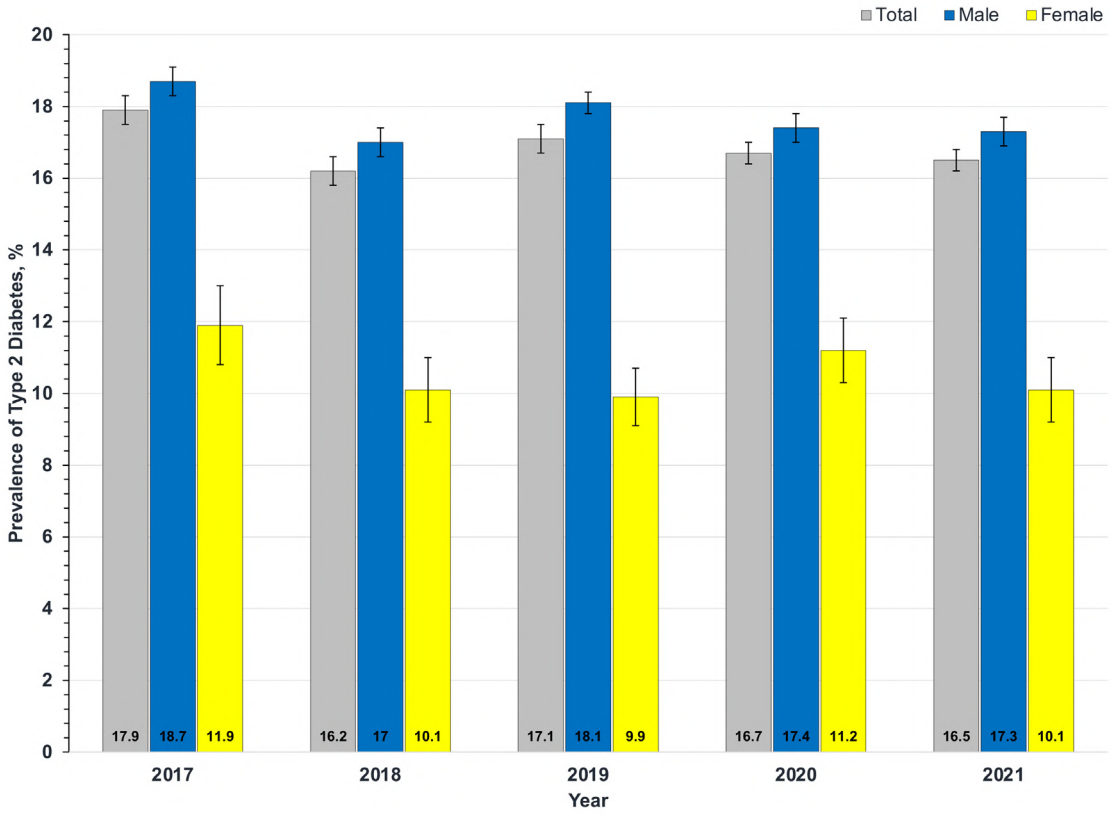

Figure 1. Trends in the age- and sex-adjusted prevalence of type 2 diabetes and 95% CI from 2017 to 2021; sex-specific prevalence (age-adjusted)

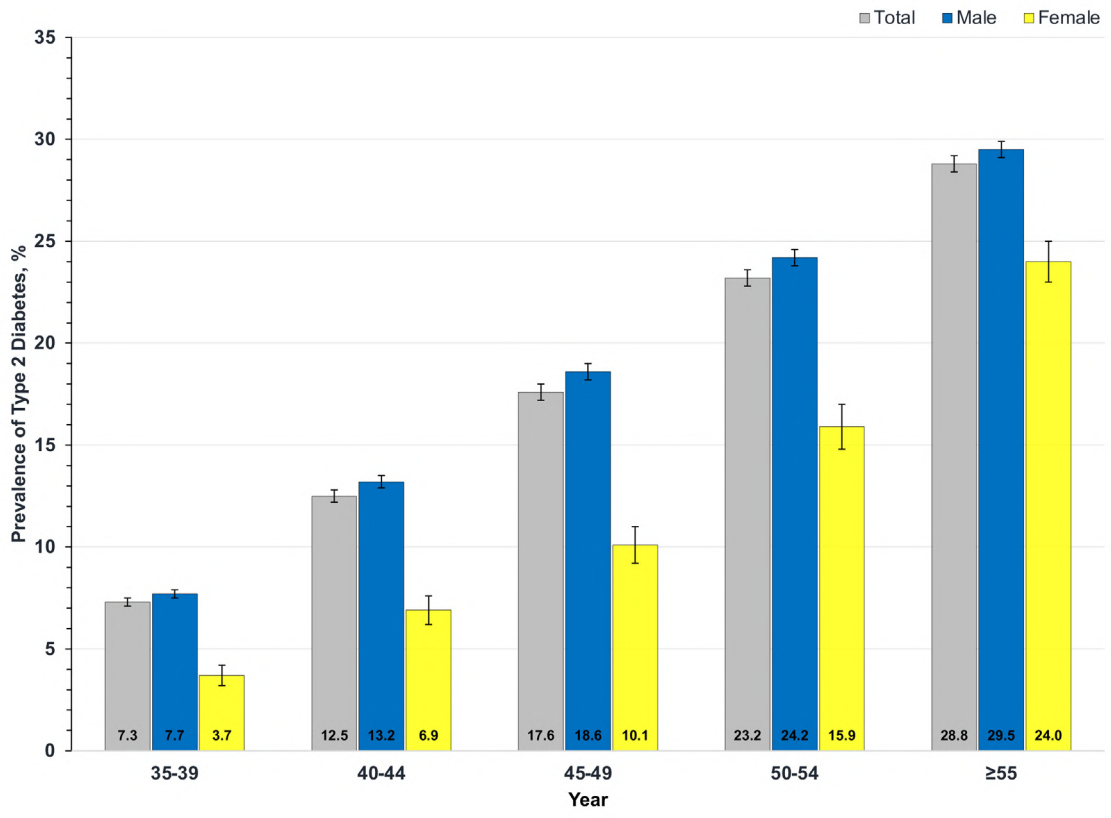

Figure 2. Prevalence of type 2 diabetes and 95% CI, stratified by age and sex

Table 2. Prevalence of type 2 diabetes among Royal Thai Army personnel from 2017-2021

Characteristics	Overall (n=235,491)		2017 (n=39,899)		2018 (n=45626)		2019 (n=51208)		2020 (n=53004)		2021 (n=45754)		*p*-for trend
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Total [a]	18.4	18.3-18.6	17.9	17.5-18.2	16.2	15.8-16.5	17.1	16.8-17.5	16.7	16.3-17.0	16.5	16.1-16.8	0.001†
Sex [b]													
Male	17.6	17.4-17.8	18.7	18.3-19.1	17.0	16.6-17.3	18.1	17.8-18.5	17.4	17.0-17.7	17.3	16.9-17.7	0.001†
Female	11.3	11.0-11.7	11.9	10.9-13.0	10.1	9.4-11.0	9.9	9.1-10.7	11.2	10.5-12.0	10.1	9.2-11.0	0.218‡
Age (years) [c]													
35-39	7.3	7.0-7.5	9.0	8.3-9.7	6.8	6.3-7.4	7.8	7.3-8.3	6.5	6.1-7.0	6.5	6.0-6.9	<0.001†
40-44	12.5	12.2-12.8	13.6	12.8-14.4	11.5	10.9-12.2	13.0	12.4-13.7	11.5	10.9-12.2	12.4	11.7-13.1	0.061‡
45-49	17.6	17.2-18.0	18.4	17.5-19.4	16.3	15.5-17.2	17.9	17.0-18.7	17.3	16.5-18.1	17.4	16.6-18.2	0.554‡
50-54	23.2	22.8-23.6	24.2	23.3-25.0	22.2	21.4-23.0	23.4	22.6-24.2	23.3	22.5-24.2	23.2	22.2-24.1	0.538‡
≥55	28.8	28.4-29.2	29.0	28.1-29.9	28.4	27.5-29.2	28.5	27.7-29.3	29.7	29.0-30.5	28.6	27.7-29.5	0.557‡
Regions [a]													
Bangkok	17.0	16.7-17.4	17.3	16.4-18.2	16.0	15.3-16.7	16.8	16.1-17.6	18.0	17.2-18.7	18.4	17.4-19.4	<0.001†
Central	16.9	16.6-17.1	20.1	19.4-20.7	16.6	16.1-17.2	17.7	17.2-18.3	16.1	15.6-16.6	15.3	14.8-15.9	<0.001†
Northeast	17.2	16.9-17.6	16.8	16.0-17.7	17.1	16.3-18.0	18.4	17.5-19.2	17.7	16.9-18.4	19.8	18.9-20.7	<0.001†
North	18.3	17.9-18.7	17.0	16.2-17.8	16.5	15.5-17.5	18.0	17.2-18.9	18.5	17.5-19.4	18.6	17.7-19.4	0.001†
South	13.4	13.0-13.9	13.1	11.9-14.3	13.0	12.2-13.9	12.6	11.8-13.5	11.9	11.1-12.8	10.0	9.2-10.9	<0.001†

95% CI: 95% confidence interval, †Nonlinear trend was tested first by adding a quadratic term into the regression model. If not significant, linear trend was tested., ‡Linear trend, [a]age- and sex- adjusted prevalence, [b]age-adjusted prevalence, [c]sex-adjusted prevalence

Table 3. Factors associated with type 2 diabetes among Royal Thai Army personnel

Factors	Unadjusted Prevalence Ratio	95% CI	*p*-value	Adjusted Prevalence Ratio	95% CI	*p*-value
Sex						
Female	1			1		
Male	1.50	1.45-1.55	<0.001	1.11	1.07-1.15	<0.001
Age (years)						
35-39	1			1		
40-44	1.71	1.65-1.79	<0.001	1.45	1.40-1.51	<0.001
45-49	2.41	2.32-2.51	<0.001	1.84	1.77-1.91	<0.001
50-54	3.19	3.08-3.31	<0.001	2.24	2.16-2.31	<0.001
≥55	3.95	3.81-4.09	<0.001	2.60	2.52-2.69	<0.001
Regions						
Bangkok	1			1		
Central	0.96	0.93-0.98	<0.001	0.90	0.88-0.92	<0.001
Northeast	1.01	0.98-1.04	0.515	0.91	0.89-0.93	<0.001
North	0.99	0.97-1.02	0.697	0.95	0.93-0.98	<0.001
South	0.71	0.69-0.74	<0.001	0.74	0.72-0.77	<0.001
Health insurance scheme						
Civil servant medical benefit	1				1	
Social Security	0.84	0.77-0.91	<0.001	1.03	0.96-1.11	0.462
Universal Coverage	0.72	0.63-0.81	<0.001	0.83	0.75-0.92	<0.001
Smoking status						
Never	1			1		
Ex-smoker	1.36	1.33-1.38	<0.001	1.15	1.13-1.17	<0.001
Current smoker	1.08	1.06-1.10	<0.001	1.12	1.10-1.14	<0.001
Alcohol consumption						
Never	1			1		
Ex-drinker	1.33	1.29-1.37	<0.001	1.17	1.14-1.20	<0.001
Current drinker	1.15	1.12-1.17	<0.001	1.03	1.01-1.05	0.010
Regular exercise						
No	1			1		
Yes	0.85	0.83-0.86	<0.001	0.89	0.87-0.90	<0.001
Body mass index (kg/m^2)						
18.50-22.99	1			1		
<18.50	0.91	0.81-1.01	0.090	0.95	0.86-1.05	0.275
23.00-24.99	1.48	1.44-1.53	<0.001	1.26	1.22-1.29	<0.001
25.00-29.99	2.16	2.10-2.22	<0.001	1.57	1.53-1.61	<0.001
≥30.00	3.46	3.36-3.56	<0.001	2.21	2.15-2.27	<0.001
Hypertension comobidity						
No	1			1		
Yes	5.25	5.14-5.37	<0.001	3.97	3.88-4.05	<0.001

Table 3. Factors associated with type 2 diabetes among Royal Thai Army personnel (Cont.)

Factors	Unadjusted Prevalence Ratio	95% CI	*p*-value	Adjusted Prevalence Ratio	95% CI	*p*-value
Year						
2017	1			1		
2018	0.88	0.86-0.91	<0.001	0.94	0.92-0.96	<0.001
2019	0.93	0.91-0.96	<0.001	0.99	0.97-1.01	0.384
2020	0.91	0.89-0.93	<0.001	0.95	0.92-0.97	<0.001
2021	0.87	0.84-0.89	<0.001	0.91	0.89-0.94	<0.001

Multivariable model included sex, age, regions, health scheme, smoking status, alcohol consumption, regular exercise, body mass index, hypertension, and year
95% CI: 95% confidence interval

that among females in all age groups between 35 and 60 years which was in line with the recent report from the IDF Atlas in 2019.[13] However, the NHES VI in 2019 represented that T2D prevalence among Thai men aged 30 to 44 years was higher than that among women, whereas, among adults aged 45 to 59 years, females revealed a higher prevalence of T2D than males.[1] We found that RTA personnel residing in Bangkok were more likely to have T2D than those residing in other regions, consistent with the findings from the NHES VI [1]. This phenomenon may be explained by the recent evidence that the RTA personnel in Bangkok tended to have a higher prevalence of obesity than those in other regions.[4]

Our finding indicated a dose-response relationship between the age of study participants and T2D prevalence among both males and females. This finding agreed with the related study in Thailand[14] and the IDF Atlas in 2019.[13] The established evidence can explain this finding that aging directly affects the decline of β-cell function and contributes indirectly to impaired insulin sensitivity through lifestyle-related and comorbidity-related risk factors.[15, 16] Our results suggest that the high prevalence of T2D among RTA personnel, especially in higher-age individuals, should be recognized and provided appropriate management, such as aligning approaches to diabetes management with the Chronic Care Model.[17, 18]

Cigarette smoking is a known independent behavioral risk factor for T2D.[19-23] Similarly, we observed that RTA personnel reporting former and current smoking tended to have higher T2D prevalence than those who never smoked. Furthermore, we also found that the prevalence of current smoking in the present study (24.7 to 29.0%) was higher than that among Thai adults (18.7%) reported in the NHES VI.[1] Therefore, cigarette smoke may significantly contribute to T2D among RTA personnel. Our study suggests that advising to discontinue cigarette smoking and providing tobacco cessation support should be incorporated during annual physical health examinations.[24]

Our study demonstrated that the T2D prevalence among study participants who consume alcohol was higher when compared with that among abstainers. Similarly, the Atherosclerosis Risk in Communities Study also indicated an increased risk of T2D was observed among men consuming >21 drinks/week compared with men consuming ≤1 drink/week (AOR 1.50; 95% CI 1.02 to 2.20).[25] In contrast, a large population-based cohort study in Denmark reported that consuming alcohol over three to four days weekly is associated with the lowest risk of diabetes compared with consuming <1 day/week.[26] However, the existing evidence demonstrated that chronic use of alcohol is considered a potential risk factor for T2D, for which several mechanisms, such as defective glucose tolerance and decreased insulin sensitivity among individuals with chronic alcohol use, may explain.[27,28]

Our finding also indicated that the prevalence of current alcohol consumption among RTA personnel (62.6 to 66.8%) was higher than among Thai civilians (44.6%) in the NHES VI. [1] Therefore, current alcohol consumption may play an essential role in contributing to T2D in this study population. Our study suggested that alcohol consumption was a potential behavioral risk factor for T2D. Thus, reducing or stopping alcohol consumption should be encouraged to attenuate the prevalence of T2D and alleviate its complication.[29-31] According to the cultural context among RTA personnel, reduced harmful use of alcohol may be a priority.[32] Therefore, a pattern of alcohol consumption should be assessed in annual physical health examinations. Then brief interventions such as Negotiated Interviews to encourage clients to change their risky behaviors should be contributed.[33]

In line with existing literature [34, 35], obesity is a well-known risk for T2D. Our findings demonstrated that T2D was associated with higher BMI, especially among the RTA personnel with a BMI greater than or equal to 5 kg/m^2, consistent with related studies in the US[36], China[37, 38] and India.[39] Additionally, a recent study in Thailand reported a rising trend in obesity prevalence among RTA personnel from 2017 to 2021, especially those aged less than 50 years.[4] Thus, our study suggested that weight management through lifestyle change, including a healthy diet and physical exercise, should be encouraged for RTA personnel. [40-42]

We observed that the prevalence of T2D among RTA personnel reporting regular exercise was significantly lower than that among those with sedentary behavior. This finding was comparable with the Da Qing IGT and Diabetes Study, indicating that exercise intervention significantly reduced the incidence of diabetes over six years among those with IGT.[42] Therefore, our study suggested that regular exercise and progressive resistance training should be encouraged in this population.[42, 43] Vigorous exercise rarely causes heat injuries and cardiovascular events,[44,45] and physical exercise should be performed appropriately based on related guidelines. [46]

Compared with RTA personnel without HT comorbidity, we found that those with existing HT had a higher T2D prevalence. This observation was likely due to the well-documented positive relationship between HT and T2D.[38, 47, 48] T2D and HT are closely interlinked because of shared mechanisms and risk factors, for example, inappropriate activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, vascular inflammation, arterial remodeling and obesity.[3, 34] Thus, effective programs should target individuals with HT, including nonpharmacologic treatment [49, 50] and appropriate pharmacologic therapy. [3, 51, 52]

This study provided valuable insights into the prevalence of T2D and its associated factors in Thailand, representing a large sample size of RTA personnel. These data help produce strategies for the primary prevention of T2D and its complications, such as ASCVD, in this population. However, further study on longitudinal analysis to explore the long term effect and time-varying risk factors for type 2 diabetes is needed.

This study encountered several limitations. First, the study was a serial cross-sectional study; therefore, the results could present only an association between T2D and its associated factors. Second, approximately 90% of study participants were male RTA personnel; however, the results demonstrated the actual situation in this study population. Third, information on lifestyle factors was collected using the questionnaires. Therefore, the recall bias could have occurred. Fourth, some variables were collected very broadly, for example, the intensity and frequency of alcohol consumption. In addition, the present study did not collect the intensity and frequency of tobacco use. Similarly, we needed more detailed data on the intensity, frequency or type of exercise. Fourth, we used the collected data health examination database; thus, data on some behavioral factors needed to be included, such as smoking status (2.1%), alcohol consumption (1.7%) and regular exercise (2.0%). However, this study comprised a large sample size, so the existing data would be included in the analysis. Thus, available data provided valuable evidence regarding

the associations between these behavioral factors and the prevalence of T2D.

Conclusion

Our study indicated that T2D is a common health issue, especially among males, higher-aged participants and RTA personnel residing in Bangkok and the northeast. Cigarette smoking, alcohol consumption and sedentary behavior played an essential role in the prevalence of T2D in this population. Furthermore, obesity and HT comorbidity were related to T2D.

Abbreviations

T2D: type 2 diabetes, HT: Hypertension, NCDs: Noncommunicable diseases, ASCVD: Atherosclerotic cardiovascular diseases, BMI: Body mass index, FPG: Fasting plasma glucose, BP: blood pressure, RTA: Royal Thai Army, RTAMED: Royal Thai Army Medical Department, NHES: National Health Examination Survey, APR: Adjusted prevalence ratio, CI: Confidence interval, SD: standard deviation

Consent for publication

This manuscript includes details and images unrelating to any individual.

Data availability

The data supporting this study's findings are available from the Royal Thai Army Medical Department, Bangkok, Thailand. Still, restrictions apply to the availability of these data, which were used under license for the current study, and are publicly available. However, data are available from the authors upon reasonable request and with permission of the Royal Thai Army Medical Department, Bangkok, Thailand (contact Boonsub Sakboonyarat via boonsub 1991@pcm.ac.th).

Competing interests

The authors declare that they have no competing interests.

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TRIMETHOPRIM-SULFAMETHOXAZOLE FOR *PNEUMOCYSTIS JIROVECII* PNEUMONIA PROPHYLAXIS AMONG HIV-POSITIVE PATIENTS IN THE ERA OF EARLY ANTIRETROVIRAL THERAPY INITIATION

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Abstract

Background: Trimethoprim-Sulfamethoxazole (TMP-SMX) is currently recommended for the primary prevention of *Pneumocystis jirovecii* pneumonia (PCP) among HIV-positive patients whose CD4 count is less than 200 cells/mm^3. However, adverse drug reactions (ADR) have been reported among some patients. In the era of early antiretroviral therapy (ART) initiation, the prevalence of PCP has gradually decreased. Therefore, to avoid unnecessary ADR, TMP-SMX might be less beneficial when the patient receives early ART initiation.

Objectives: The study aimed to evaluate the incidence of PCP, all-cause mortality, CD4 count at 6 months after ART, other opportunistic infections (OIs), and ADRs among HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis.

Methods: This retrospective cohort study was conducted in Ratchaburi Hospital between January 2014 and February 2022. HIV-positive patients with an initial CD4 count <200 cells/mm^3 or <14% and receiving early ART initiation within 2 weeks after HIV diagnosis were investigated. Patients with and without TMP-SMX prophylaxis were analyzed in terms of baseline characteristics, the incidence of PCP, all-cause mortality, other OIs and ADRs from TMP-SMX. The ratio of TMP-SMX vs. no TMP-SMX groups was 2:1.

Results: In total, 230 HIV-positive patients presenting an initial CD4 count <200 cells/mm^3 or <14% were included in this study. All patients received early ART initiation within 2 weeks after HIV diagnosis and showed good adherence. The incidence of PCP in the TMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and in the no prophylaxis group was 3 of 77 cases (3.89%), OR 0.329; 95% CI, (0.053 – 1.998); p=0.226. CD4 count at 6 months after ART initiation significantly increased in the no prophylaxis group (277.4 vs. 179.5 cells/mm3; mean difference 97.92; 95% CI of difference, (65.15-130.69); p <0.001). All-cause mortality and other bacterial and OIs did not differ between the two groups. All adverse events from TMP-SMX were minor rashes, 13 of 153 cases (8.5%).

Conclusion: Among HIV-positive patients receiving early ART initiation, the incidence of PCP revealed no difference between with and without TMP-SMX prophylaxis. All-cause mortality and rate of OI were also comparable between the 2 groups.

Keywords: HIV, Early antiretroviral therapy, *Pneumocystis jirovecii* pneumonia, Trimethoprim-Sulfamethoxazole, Prophylaxis

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Introduction

Currently, HIV can be diagnosed quickly and accurately. Anti-retroviral agents are more effective with fewer side effects and more accessibility, resulting in better quality of life and longer life expectancy.[1, 2] However, some HIV-positive patients, with low CD4 count, experience opportunistic infections (OIs) due to delayed diagnosis and treatment.

The most common OIs among HIV-positive patients are tuberculosis, *Pneumocystis jirovecii* pneumonia (PCP), and cryptococcal meningitis.[1, 3] The incidence of PCP in the era before ART was 80 cases/1,000 population/year and decreased to 40 cases/1,000 population/year after introducing ART.[4]

According to the current guidelines on HIV treatment and prevention. PCP prophylaxis is recommended among HIV-positive patients with CD4 count <200 cells/mm^3 and can be discontinued either when the CD4 count is >200 cells/mm3 for at least three consecutive months or between 100 and 200 cells/mm3 with undetectable serum HIV RNA for three to six months.[5] Trimethoprim-Sulfamethoxazole (TMP-SMX) is a highly effective drug for PCP prophylaxis. However, serious adverse drug reactions (ADRs) have also been frequently reported.[6-8]

From related studies, comparing prophylaxis versus no prophylaxis groups, the prevalence of PCP did no significantly differ among HIV-positive patients already receiving ART.[9-12] However, a comparative study has not been conducted in Thailand. Therefore, to avoid ADRs from TMP-SMX, we hypothesized no difference in PCP prevalence PCP between TMP-SMX prophylaxis and nonprophylaxis groups when patients received early ART initiation. This study aimed to evaluate the incidence of PCP among HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis.

Methods

This study was reviewed and approved by the Institutional Review Boards of Ratchaburi Hospital, Thailand (COA-RBHEC 027/2023). This retrospective cohort study was conducted in the HIV Clinic, Ratchaburi Hospital between January 2014 and February 2022. According to Teshale et al.,[9] the incidence of PCP was 5.2/100 persons-year in the prophylaxis group and 19.2 /100 persons-year in the never started prophylaxis group. Thus, the sample size in this study was 139 and 70, respectively. When considering a 10% dropout rate, the sample size was 153 cases in the TMP-SMX group and 77 cases in the nonTMP-SMX group.

HIV-positive patients aged at least 18 years old with an initial CD4 count <200 cells/mm^3 or <14% and receiving early ART initiation within two weeks after HIV diagnosis were eligible for this study. The patients were excluded if they had prior PCP, poor ARV adherence, and had already received drugs other than TMP-SMX for PCP prophylaxis. Patients with and without TMP-SMX prophylaxis were analyzed in terms of baseline characteristics, the incidence of PCP, all-cause mortality, other OIs and ADRs from TMP-SMX.

Data collection

The patient's clinical and laboratory parameters were collected from the hospital electrical database (HOSxP). Baseline characteristics included age, sex, initial CD4 count, co-infection, OIs and co-morbidity and initial laboratory investigation at the time of HIV diagnosis.

Definitions

Parameters in this study are defined as the following; HIV positive status was defined as having three positive serum anti-HIV testing results.[13] *Pneumocystis jirovecii* pneumonia was diagnosed using clinical settings including signs, symptoms and chest X-ray compatible with PCP infection (bilateral symmetrical interstitial infiltration) with one of the following diagnostic methods[5, 14]: positive for *Pneumocystis jirovecii* from sputum smear, bronchoalveolar lavage or positive biopsy using GMS staining, direct immunofluorescent staining or Polymerase Chain Reaction for PCP or symptoms improving after empirical treatment of PCP.

Early ART initiation was defined as receiving ART within two weeks after HIV diagnosis. Under the current HIV guidelines, either rapid

ART initiation within seven days or same-day ART was recommended. However, for those positive for OIs, we chose two weeks as the optimal timing of early ART initiation in this study.[13, 15]

Adherence was defined as "good" at ≥95% e.g., <2 doses of 30 doses or <3 doses of 60 doses were missed. Between 85 and 94% was defined as "poor" (3 to 5 doses of 30 doses or 3 to 9 doses of 60 doses were missed) as documented by the ART healthcare provider. [16]

Minor drug rash was defined as mild cutaneous reactions to drugs not seriously compromising clinical conditions and early improvement with full recovery. [17]

Outcome assessment

The primary outcome was to evaluate the incidence of PCP in HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis. The secondary outcome was to evaluate all-cause mortality, CD4 count at six months after ART, other bacterial and OIs and ADRs from TMP-SMX.

Statistical analysis

Categorical variables were reported as frequencies and percentages. Mean ± standard deviation was used for normally distributed continuous variables and median with interquartile range (percentile 25 and 75) for nonnormally distributed variables. The normality of the distribution of variables was examined using the Kolmogorov-Smirnov test. For demographic data, categorical variables were compared using chi-square or Fisher's exact test and continuous variables were compared using the Mann-Whitney U test.

To compare the incidence of PCP infection between the two groups, univariate analysis was performed and reported by odds ratio (OR) and 95% confidence intervals (CI). For all tests performed, a two-tailed $p<0.05$ was considered statistically significant. SPSS, Version 26.0 was used to perform all statistical analysis.

Results

From January 2014 to February 2022, 230 HIV-positive patients presenting an initial CD4 count <200 cells/mm^3 or <14% were included in this study. All patients had early ART within two weeks after HIV diagnosis with good adherence. The enrollment flowchart is shown in **Figure 1**.

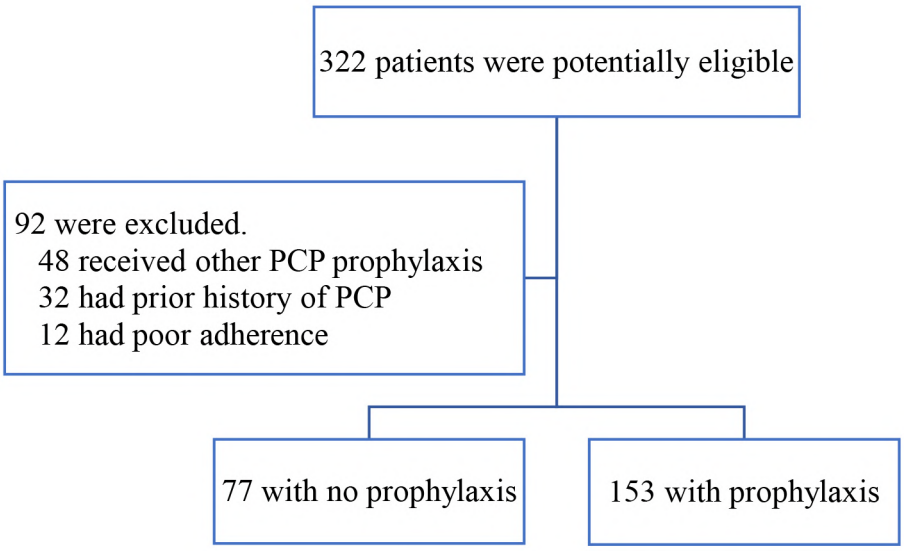

Figure 1. Enrollment flow chart of HIV-positive patients with and without prophylaxis during the study period (6-month follow-up)

The baseline characteristics of 230 patients are shown in **Tables 1 and 2.** Of 230 patients, 77 patients had no TMP-SMX and 153 patients had TMP-SMX prophylaxis. At the time of HIV diagnosis, all patients had a mean age of 38.68 ±11.65 years old and the median initial CD4 count was 77 cells/mm^3, interquartile range (IQR) = 77.00 to 157.25. Most patients were male (63.5%). In the prophylaxis group, the median initial CD4 count was significantly lower (67 vs. 139 cells/mm^3, p <0.001) and the rate of tuberculosis was higher (13.7% vs. 3.9%, p = 0.021). Other comorbidity, co-infection and initial laboratory investigation were comparable between groups. The median duration of ART initiation after diagnosis of HIV was two weeks.

PCP in the TMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and the in no prophylaxis group was 3 of 77 cases (3.89%), OR= 0.33; 95% CI, (0.05 to 1.99); p = 0.226. CD4 count at six months after ART in the no prophylaxis group was significantly increased (277.4 vs. 179.5 cells/mm3; mean difference 97.92; 95% CI of difference, (65.15 to 130.69); p<0.001). All-cause mortality and other bacterial and OIs did not differ between the two groups. All adverse events from TMP-SMX were minor rashes, 13 of 153 cases (8.5%). When performing subgroup analysis using CD4 count levels, those having CD4 count <100 cells/mm^3 revealed a higher prevalence of PCP in the nonTMP-SMX prophylaxis group (10 vs. 2.0%, respectively). However, no statistical significance was noted.

Table 1. Baseline characteristics of 230 HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Age, year [mean ± SD]	36.83 ± 11.33	39.61 ± 11.73	0.088
Male, N (%)	52 (67.5)	94 (61.4)	0.365
Initial CD4 count, cell/mm^3 [median (IQR)]	139 (63.50,239.00)	67 (29.00,125.50)	< 0.001
Initial CD4 count, % [mean ± SD]	9.05 ± 4.36	6.17 ± 4.08	< 0.001
Duration of ART initiation after diagnosis, weeks [median (IQR)]	2 (2,2)	2 (2,2)	0.090
Duration of follow-up, years [median (IQR)]	3 (1,4)	4 (3,6)	0.080
Co-infection			
Hepatitis B, N (%)	5 (6.5)	11 (7.2)	0.845
Hepatitis C, N (%)	4 (5.2)	4 (2.6)	0.447
Syphilis, N (%)	10 (13.0)	10 (6.5)	0.101
Isolated cryptococcal antigenemia, N (%)	1 (1.3)	3 (2.0)	1.000
Opportunistic infection			
No OIs, N (%)	64 (83.1)	125 (81.7)	0.791
Tuberculosis, N (%)	3 (3.9)	21 (13.7)	0.021
CMV infection, N (%)	1 (1.3)	2 (1.4)	1.000
Talaromycosis, N (%)	1 (1.3)	1 (0.7)	1.000
Histoplasmosis, N (%)	1 (1.3)	0 (0)	0.335
Candidiasis, N (%)	7 (9.1)	4 (2.6)	0.046

Table 1. Baseline characteristics of 230 HIV-positive patients receiving early ART with and without TMP-SMX for PCP prophylaxis (Cont.)

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Comorbid disease			
No disease, N (%)	63 (81.8)	108 (70.6)	0.066
CAD, N (%)	0 (0)	0 (0)	-
Hypertension, N (%)	8 (10.4)	18 (11.8)	0.756
DM, N (%)	4 ((5.2)	7 (4.6)	1.000
CKD, N (%)	1 (1.3)	0 (0)	0.335
Stroke, N (%)	1 (1.3)	0 (0)	0.335
Cirrhosis, N (%)	1 (1.3)	1 (0.7)	1.000
Other, N (%)	10 (13.0)	29 (19.0)	0.671

Abbreviations: ART, Antiretroviral therapy; CAD, Coronary artery disease; CMV, Cytomegalovirus; DM, Diabetes mellitus; CKD, Chronic kidney disease; mm3, Cubic millimeters; OIs, Opportunistic infections; PCP, Pneumocystis pneumonia; TMP-SMX, Trimethoprim-Sulfamethoxazole

Table 2. Initial laboratory investigation at the time of HIV diagnosis of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

Factors	No prophylaxis N = 77	PCP prophylaxis N = 153	*p*-value
Hb, g/dL [mean ± SD]	12.08 ± 2.40	11.74 ± 2.08	0.269
Hct, % [mean ± SD]	36.77 ± 6.82	35.59 ± 5.77	0.171
WBC, cell/mm^3 [median (IQR)]	5730 (4710, 7035)	5260 (4080, 6385)	0.053
ANC, cell/mm^3 [median (IQR)]	3280 (2370, 4566))	2856 (2164, 2856)	0.053
Platelet, cell/mm^3 [median (IQR)]	244000 (201500, 326500)	243000 (191000,303000)	0.239
BUN, mg/dL [mean ± SD]	9.93 ± 3.41	11.05 ± 5.45	0.153
Creatinine, mg/dL [mean ± SD]	0.86 ± 0.21	0.88 ± 0.44	0.721
Potassium, mmol/L [mean ± SD]	3.98 ± 0.44	4.00 ± 0.54	0.846
TB, mg/dL [median (IQR)]	0.38 (0.25, 0.53)	0.44 (0.30,0.54)	0.113
DB, mg/dL [median (IQR)]	0.20 (0.14, 0.24)	0.21 (0.15,0.28)	0.092
AST, U/L [median (IQR)]	23.50 (20.00, 30.75)	27.00 (21.00,41.00)	0.053
ALT, U/L [median (IQR)]	21.50 (16.00, 33.25)	25.00 (16.00,40.00)	0.273
ALP, U/L [median (IQR)]	80.00 (64.00, 110.00)	85.00 (71.00,117.00)	0.088
Albumin, g/dL [mean ± SD]	4.16 ± 0.51	3.95 ± 0.64	0.053
Globulin, g/dL [mean ± SD]	4.29 ± 0.76	4.34 ± 0.80	0.745

Abbreviations: ANC, Absolute neutrophil count; ALT, Alanine transaminase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; DB, Direct bilirubin; g/dL, gram per deciliter; Hb, Hemoglobin; Hct, Hematocrit; mm3, cubic millimeters; mg/dL, milligram per deciliter; mmol/L, millimole per liter; OIs, opportunistic infections; PCP, Pneumocystis pneumonia; TB, Total bilirubin; U/L, units per liter

Table 3. Primary outcome of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis.

Factor	No prophylaxis N = 77	PCP prophylaxis N = 153	OR (95% CI)	*p*-value
Primary outcome				
Incidence of PCP, N (%)	3 (3.89)	2 (1.31)	0.33 (0.05 – 1.99)	0.226

Abbreviation: PCP, Pneumocystis pneumonia.

Table 4. Secondary outcome of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

Factor	No prophylaxis N = 77	PCP prophylaxis N = 153	Mean difference or OR (95% CI of diff)	*p*-value
Secondary outcome				
Mortality at 6 months	0 (0)	1 (0.65)	-	1.000
Death from OI, N (%)	0 (0)	0 (0)	-	-
Death from other causes, N(%)	0 (0)	1 (0.65)	-	1.000
CD4 at 6 months				
CD4 count, cell/mm^3 [mean ± SD]	277.44 ± 129.96	179.52 ± 90.61	Mean difference 97.92 (65.15 - 130.69)	< 0.001
CD4 count, % [mean ± SD]	15.30 ± 5.81	11.21 ± 5.26	Mean difference 4.09 (2.59 - 5.59)	< 0.001
Other bacterial infection, N (%)				
GI, N (%)	0 (0)	1 (0.7)	-	1.000
Other infection*, N (%)	0 (0)	0 (0)	-	-
Other OIs				
Tuberculosis, N (%)	1 (1.3)	2 (1.3)	OR 1.01 (0.09 – 11.27)	0.996
Talaromycosis, N (%)	0 (0)	0 (0)	-	-
Histoplasmosis, N (%)	0 (0)	1 (0.7)	-	1.000
Toxoplasmosis, N (%)	0 (0)	0 (0)	-	-
Adverse drug reactions (ADRs) of Trimethoprim-Sulfamethoxazole				
Minor rash, N (%)	0 (0)	13 (8.5)	-	0.005
SJS/TEN, N (%)	0 (0)	0 (0)	-	-
Serious ADRs, N (%)	0 (0)	0 (0)	-	-
Nausea/Vomiting, N (%)	0 (0)	0 (0)	-	-

*Other infections: H&N, RS, CVS, GI, NS, SST, MSK, LN

Abbreviations: ADRs, Adverse drug reactions; CVS, Cardiovascular system; GI; Gastrointestinal; H&N, Head and neck; LN, Lymph node; mm^3, Cubic millimeters; MSK, Musculoskeletal; NS, Nervous system; OI, Opportunistic infection; PCP, Pneumocystis pneumonia; RS, Respiratory system; SST, Skin and soft tissue; SJS/TEN, Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis

Table 5. Subgroup analysis by CD4 count of PCP prevalence of 230 HIV-positive patients receiving early ART initiation with and without TMP-SMX for PCP prophylaxis

CD4 count, cell/mm^3	No prophylaxis N = 77	PCP prophylaxis N = 153	OR (95%CI)	*p*-value
<100	3/30 (10.0%)	2/102 (2.0%)	0.18 (0.02-1.13)	0.068
100-199	0/23 (0%)	0/48 (0%)	-	-
≥ 200	0/24 (0%)	0/3 (0%)	-	-

Abbreviation: mm^3, Cubic millimeters

Discussion

In this retrospective cohort study, from January 2014 to February 2022, the incidence of PCP in the TMP-SMX vs. the nonTMP-SMX prophylaxis group was 2 of 153 cases (1.31%) and 3 of 77 cases (3.89%) respectively, with OR 0.33; 95% CI 0.05 to 1.99; *p*= 0.226. Similar to a related study[10], this result emphasized that the incidence of PCP did not significantly increase among HIV-positive patients with early ART initiation not receiving TMP-SMX prophylaxis. Nonetheless, the incidence of failed TMP-SMX prophylaxis in this study was lower than in related studies (1.31 vs. 11%).[11, 12]

In contrast to the current guidelines on HIV treatment and prevention recommend that recommend PCP prophylaxis in all cases when patients had CD4 <200 cells/mm^3 [5, 13, 15], subgroup analysis in our study showed that all PCP patients in both groups had initial CD4 count <100 cells/mm^3 (OR= 0.18; 95% CI 0.02 to 1.13; *p* = 0.068). HIV-positive patients with an initial CD4 count >100 cells/mm^3 did not develop PCP during the study period. Similar to the related systematic review[18], the risk of PCP increased more among HIV-positive patients with CD4 <100 cells/mm^3 compared with CD4 count between 101 and 200 cells/mm^3. Furthermore, the Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) study[19] investigated the safety of discontinuation of PCP prophylaxis among patients with CD4 <200 cells/mm^3 receiving virological suppression. The event rate of PCP among HIV-positive patients with CD4 counts between 101 and 200 cells/mm^3 with or without TMP-SMX prophylaxis was similar. Therefore, discontinuing PCP prophylaxis in this group might also be safe when their serum HIV RNA was undetectable. However, from the COHERE study, when patients had CD4 <100 cells/mm^3, PCP prophylaxis could significantly reduce the incidence of PCP, which was similar to other related studies.[9, 10] In contrast to ours, among patients with CD4 <100 cells/mm^3, the incidence of PCP was not statistically significant between groups (but tended to increase in the nonprophylaxis group 10 vs. 2%). This might have been due to the small sample size when performing subgroup analysis. These data could imply that even early initiating ART within two weeks, PCP prophylaxis might be essential among patients with CD4 <100 cells/mm^3 but not in the group with CD4 >100 cells/mm^3.

The mortality rate at six months between groups did not differ; however, we did not calculate the sample size for this secondary outcome. Interestingly, the mean CD4 count at six months after ART initiation in the nonTMP-SMX prophylaxis group increased higher than the other (277.4 vs. 179.5 cells/mm^3; mean difference 97.92; 95% CI of difference, (65.15 to 130.69); *p*<0.001). However, this finding had to be interpreted carefully due to the significantly lower initial CD4 count in the prophylaxis group posing a potential bias in our study.

Thirteen of 153 cases (8.5%) in the TMP-SMX group reported minor drug rash. No other

ADRs were found in this study. This could have stemmed from the high prevalence of TMP-SMX hypersensitivity reaction in Thailand, 1 to 3% in the general population and up to 34% among patients with HIV.[6]

Our study possessed two strengths: the complete medical records in our electronic database, and the benefit from data collection. However, this study encountered some limitations. First, our study constituted a retrospective cohort. Second, the sample size in the nonTMP-SMX prophylaxis group was small (77 patients). Third, this study was conducted in a single center; our patients might not represent the general population in Thailand. Fourth, the definition of early ART initiation in this study was two weeks from HIV diagnosis, which was still late compared with the current HIV guidelines promoting the same-day or rapid ART initiation within seven days. Fifth, potential bias was shown in baseline characteristics; a significantly lower initial CD4 count in the prophylaxis group was noted. This could have affected the incidence of PCP and CD4 levels six months after ART initiation. Therefore, future studies should be conducted prospectively matching baseline CD4 count between groups and conducted among patients receiving the same day or rapid ART within seven days after HIV diagnosis to clarify the true results and whether it would be necessary to prescribe primary PCP prophylaxis when initiating early ART.

Conclusion

Among HIV-positive patients receiving early ART initiation, the incidence of PCP did not differ between groups with or without TMP-SMX prophylaxis. All-cause mortality and OI rate were also comparable between the two groups. In the non- prophylaxis group, CD4 count after ART initiation also increased higher and ADR from TMP-SMX was lower. These findings supported that TMP-SMX prophylaxis might not be necessary when we initiate early ART among HIV-positive patients presenting CD4 <200 cells/mm^3.

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Conflict of interest

The authors declare they have no conflicts of interest.

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PREVALENCE AND ASSOCIATED FACTORS OF MALNUTRITION AMONG ELDERLY PATIENTS AT AN OUTPATIENT CLINIC, COMMUNITY HOSPITAL IN THAILAND: A CROSS-SECTIONAL STUDY

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Abstract

Background: The number of Thais aged 60 and older has increased dramatically, and this trend will continue, making Thailand an increasingly aging society in the coming decades. The nutritional state of the elderly should be a major priority because it harms mortality and quality of life.

Methods: From August to September 2022, the prevalence and associated determinants of malnutrition were determined based on a survey and hospital records using the Mini Nutritional Assessment (MNA®) as a screening tool for malnutrition among the elderly attending the outpatient department at Bangkhla Hospital. Multinomial regression analysis accounted for any confounding factors yielding an adjusted odds ratio (aOR) and 95% confidence intervals (95%CI).

Results: This study enrolled a total of 91 individuals. Of these, 4.40% (95%CI= 0.01-0.11) of the participants were malnourished, while 18.70% (95%CI=0.11-0.28) were at risk of malnutrition. After controlling for potential confounding factors, a history of Covid-19 was associated with malnutrition (aOR=55.00, 95%CI= 2.70 to 1110.30), cancer (aOR= 25.80, 95%CI= 1.60-409.40) and gouty arthritis (aOR= 8.80, 95%CI= 1.20-59.60) was similarly associated with at risk of malnutrition. However, the protective effect of exercise was associated with malnutrition and risk of malnutrition, respectively (aOR= 0.04, 0.13, 95%CI= 0.00-0.80, 0.00-0.50).

Conclusion: Overall, the study emphasized the significance of addressing malnutrition which was on the rise among the elderly in community hospitals in Thailand, especially in light of the aging population. Health professionals and policymakers should be aware of the various factors associated with malnutrition and strive to implement appropriate interventions to improve the nutritional status and quality of life of the elderly.

Keywords: Malnutrition, Gouty arthritis, Cancer, History of Covid-19, Elderly, Outpatient, Thailand

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Introduction

The aging population has been increasing rapidly, especially among developing countries. It has been anticipated there will be an additional 1.4 billion elderly people by 2030 and 2.1 billion by 2050. According to the Institute for Economic Research on ASEAN and East Asia (ERIA), the percentage of people aged 60 and older could reach two thirds by 2040.[1] In 2020, Thailand's elderly population was projected to be 12 million or 18.3% of the entire population, or 1 in 5 individuals, six times the ratio in the prior 50 years.[2] Consequently, Thailand, possesses the fastest rate of population aging and addressing the health requirements of the elderly is one of the country's top policy priorities. Various factors influence the health of the elderly, yet nutrition remains disregarded. [3]

Malnutrition is used to characterize the situations of undernutrition, overnutrition and nutritional imbalance contributing to body dysfunction and negative clinical consequences, despite the lack of a precise definition of its etiology.[4] there is no universal agreement about its definition, prevalence, or method of identification and report. Fifteen definitions of malnutrition were critically examined to assess their variability. They ranged from descriptions of undernutrition alone to under- and overnutrition, with intakes ranging from dietary protein and energy alone to dietary and nondietary sources of all nutrients and energy. Definitions also varied from non-outcome based to those based on functional, physiological, and/or clinical outcomes. Some definitions relied on the pathways by which malnutrition develops, with one apparently requiring loss of fat-free mass. Also examined were nutrition screening tools, diversely developed for detection of malnutrition, management of malnutrition, and prediction of clinical outcomes or health care usage. Their intended use also varied from specific care settings (hospital, community, care homes Despite this, malnutrition was associated with several consequences including impaired immunity, an increased risk of falling and a deterioration in physical and cognitive performance. Furthermore, immune insufficiency may heighten illness severity, complications, recovery time and susceptibility to infections including the quality of life and the mortality rate.[5,6] there is no universal agreement about its definition, prevalence, or method of identification and report. Fifteen definitions of malnutrition were critically examined to assess their variability. They ranged from descriptions of undernutrition alone to under- and overnutrition, with intakes ranging from dietary protein and energy alone to dietary and nondietary sources of all nutrients and energy. Definitions also varied from non-outcome based to those based on functional, physiological, and/or clinical outcomes. Some definitions relied on the pathways by which malnutrition develops, with one apparently requiring loss of fat-free mass. Also examined were nutrition screening tools, diversely developed for detection of malnutrition, management of malnutrition, and prediction of clinical outcomes or health care usage. Their intended use also varied from specific care settings (hospital, community, care homes This ailment also impairs the elderly's physical and cognitive performance, resulting in hospitalization and additional expenses.[7,8] there is no universal agreement about its definition, prevalence, or method of identification and report. Fifteen definitions of malnutrition were critically examined to assess their variability. They ranged from descriptions of undernutrition alone to under- and overnutrition, with intakes ranging from dietary protein and energy alone to dietary and nondietary sources of all nutrients and energy. Definitions also varied from non-outcome based to those based on functional, physiological, and/or clinical outcomes. Some definitions relied on the pathways by which malnutrition develops, with one apparently requiring loss of fat-free mass. Also examined were nutrition screening tools, diversely developed for detection of malnutrition, management of malnutrition, and prediction of clinical outcomes or health care usage. Their intended use also varied from specific care settings (hospital, community, care homes In Thailand, the prevalence of malnutrition among the elderly ranged from 6 to 10%, while the prevalence among hospitalized elderly ranged from 40 to 70%. [9] Studies reported

that the prevalence of malnutrition in community-dwelling settings or geriatric outpatient clinics was approximately 20 and 30%, respectively. [10, 11] In addition, malnutrition and risk of malnutrition among patients at outpatient clinics and tertiary care hospitals in Thailand were 8 and 35%, respectively.[12] Even though multiple studies have investigated elderly malnutrition, a lack of information remains noted at community hospitals where primary health care was provided in Thailand. [13-17] This study aimed to determine the prevalence and associated factors of malnutrition among elderly patients at an outpatient clinic in a community hospital, illustrative of the rural community concerns in Thailand.

Methods

Study design and subjects

This cross-sectional study was conducted in August and September 2022 at Bangkhla Hospital, Chachoengsao Province, central Thailand. Patients over 60 who could make decisions freely and visited outpatient clinics were included in the study. Those who could not make judgments due to physical or mental incapacity and those who refused to participate were excluded. Participants who expressed discomfort while answering questions or being measured during the interview were excluded from the study. In addition, their arm and calf circumferences, body weight and height were measured. This study was approved by the Institutional Review Board of the Medical Department of the Royal Thai Army (IRBRTA): M019q/65.

Data collection and measurements

A computerized search of medical records was conducted to identify potential participants. Before performing the investigation, informed consent was obtained. If a participant could not read the information sheet, a research team member would read the information to them, after which they would use their fingerprint to affirm their agreement with the consent form. To obtain information from geriatric patients, face-to-face interviews using standardized questionnaires were conducted by well-trained interviewers.

The standardized questionnaire included demographic characteristics (sex, age, nationality, healthcare coverage scheme, religion, occupation, education level and monthly family income) as well as comorbidities (allergy/asthma, gouty arthritis, diabetes mellitus, dyslipidemia, thalassemia/anemia, hypertension, chronic kidney disease, all types of cancer history, disability status, Chronic Obstructive Pulmonary Disease (COPD), heart disease, thyroid disorder and history of COVID-19) which were defined based on the recorded International Classification of Diseases 10th Revision (ICD-10). In addition, current medications (antihypertensives, statins, heart failure medication, thyroid medication and antidepressants) were recorded, as well as lifestyle (living alone, living with family and exercise status obtained rom the face-to-face interview) and dietary preferences (eating habits in the previous three months, homemade or purchased food and nutrition supplements), and the MNA® questionnaire. According to the ICD-10, participants with abnormalities of the thyroid gland function or structure and symptoms related to elevated or decreased plasma concentrations of thyroid hormone (hyperthyroidism or hypothyroidism, respectively) were considered to have a thyroid disorder.

The well-trained research teams evaluated the anthropometric measurements. The participant's weight and height were determined using a mechanical scale and a stadiometer according to the Centers for Disease Control and Prevention (CDC) instructions with two decimals measurements. [18] Arm circumference was determined by placing a measuring tape at the midpoint of the acromion and olecranon processes on the shoulder blade and ulna.[19] Calf circumference measurements were taken with participants seated with their knees bent at a 90-degree angle,[20] and arm and leg circumferences were measured to one decimal place. The participant's body weight was measured in kilograms and the height in centimeters. BMI was calculated as body weight in kilograms divided by height in weight (kg)/height $(m)^2$. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). BMI scores were

classified in four groups, including<18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal range), 25.0 to 29.9 kg/m^2 (overweight) and 30.0 kg/m^2 (obese).[21]

Nutritional status definition

This study used the Mini Nutritional Assessment (MNA®) as a screening tool for malnutrition, consisting of six screening questions and twelve nutritional questions. Patients scoring 24.0 or more were defined as having a normal nutritional status, and those scoring 17.0 to 23.5 (scoring system ends withone1 a decimal of 0 or 5) were at risk of malnutrition while those scoring <17.0 were malnourished. In addition, the summation of n malnutrition (MNA® <17.0) and at risk of malnutrition (MNA® 17.0 to 23.5) was defined as the overall risk of malnutrition.[22]

Sample size and statistical analysis

The sample size was determined using the n4studies Software (Version 1.4.1) and the formula for infinite population proportion, derived from data on malnutrition prevalence in Thailand from a related study.[9] side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc.

The data were analyzed using IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp.). A number and a percentage represented the categorical information, whereas the continuous variable was represented by means and standard deviation (SD). The Chi-square test was used to compare the frequency distribution of categorical variables across strata. Using the Kolmogorov-Smirnov test, the normality of the continuous data was determined. Student's t-test was applied to compare continuous, normally distributed data. The prevalence was examined using descriptive statistics and provided as a percentage and a 95% confidence interval (CI). Independent variables were established using univariable and multivariable binary and multinomial logistic regression analyses. The overall risk of malnutrition was analyzed using binary logistic regression while. In contrast, nomial logistic regression was used to analyze the associated factors between malnutrition and normal groups and at risk of malnutrition and normal groups. Factors showing $p<0.2$ in the unadjusted analysis were entered in the multivariable analysis of binary logistic regression and multinomial logistic regression analyses.

Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were then reported, and $p<0.05$ was considered statistically significant.

Results

As shown in **Figure 1**, 105 individuals were screened for study participation. Seven were excluded due to physical impairment and having legal representatives, two declined participation, and five were excluded due to mental impairment (two psychiatric problems and three Alzheimer's disease diagnoses, respectively). Thus, 91 individuals enlisted in the study, and each participant completed the questionnaire, anthropometric measurement, MNA® nutritional status and hospital database ICD-10 recording.

The baseline characteristics of the individuals are shown in **Table 1**. The average age of participants was 70.50 ± 6.90 years, 40.70% were male, and most participants were Thai and Buddhist. Of these, 85.71% had Universal Health Coverage Scheme, and 14.29% had Civil Servant Medical Benefit Scheme. Body mass index (BMI) categorized 29.70% as pre-obese (25.00 to 29.90 kg/m^2), 28.60% were normal weight (BMI 18.50 to 22.90 kg/m^2), 24.20% were overweight (BMI 23.00 to 24.90 kg/m^2), 11% were obese (BMI ≥30.00 kg/m^2) and 6.60% were underweight (BMI <18.50 kg/m^2).

The MNA® screening revealed that 4.40% (95%CI: 0.01-0.11) of the participants were malnourished and 18.70% (95%CI=0.11-0.28) were at risk for malnutrition. As shown in **Table 2**, the overall risk of malnutrition was 23.10% (95%CI=0.15-0.33).

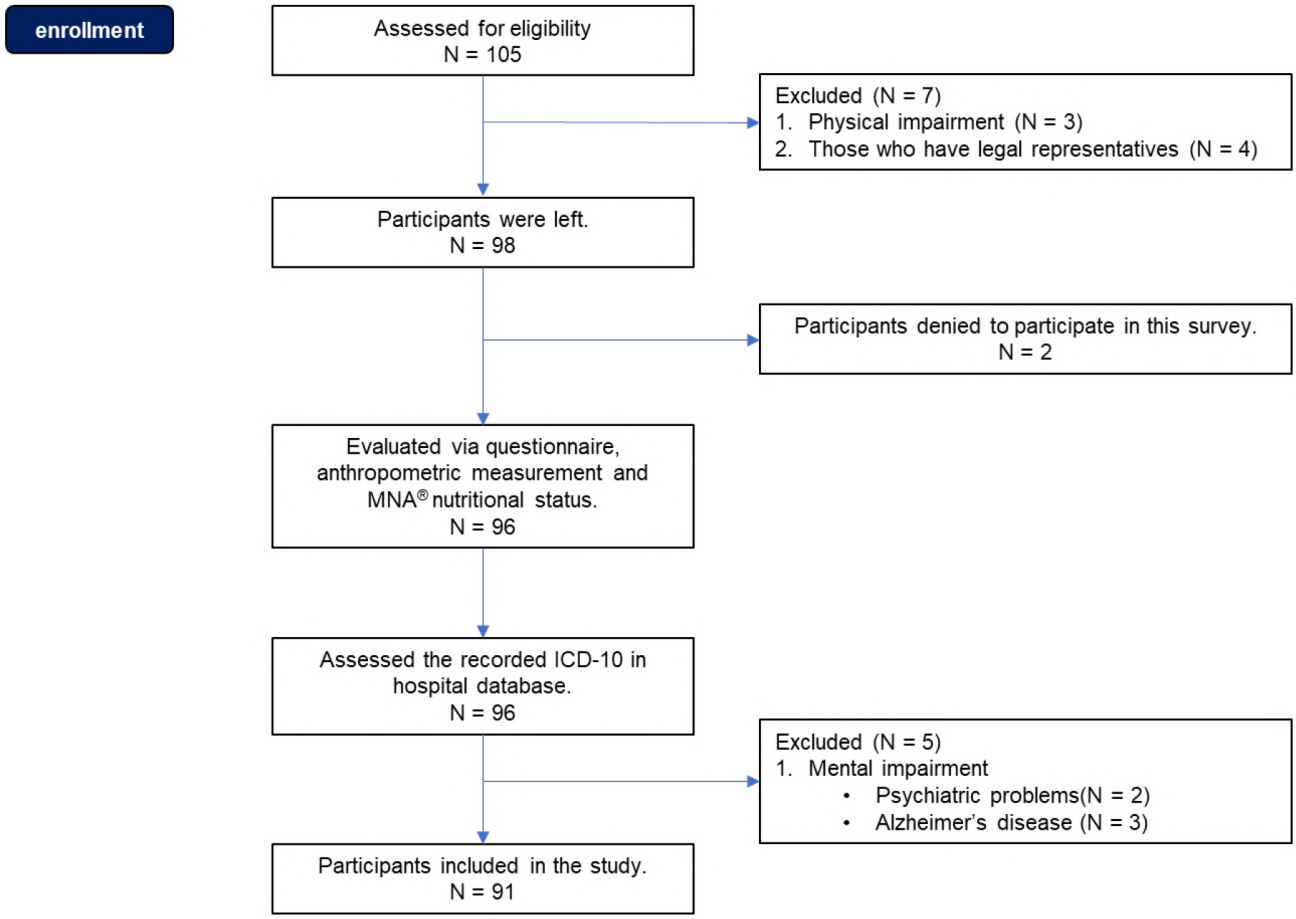

Figure 1. Flow diagram depicting the design of the cross-sectional study conducted among elderly patients at an outpatient clinic, a community hospital in Thailand.

Table 3 shows the differentials of nutritional status by participants' background characteristics and univariable binary analysis, consequently with multivariable binary analysis of potentially associated factors. The findings indicated only three factors, i.e., exercise (Adjusted Odds ratio (AOR)= 0.10, 95%CI= 0.00- 0.40), all types of cancer (aOR= 27.50, 95%CI=1.40-521.60) and history of COVID-19 (aOR= 14.30, 95% CI= 1.90-106.80), were significantly associated with malnutrition.

Table 4 shows multivariable multinomial logistic analysis revealing that after adjusting confounding factors, history of COVID-19 had an association with malnutrition (aOR= 55.00, 95% CI= 2.70-1110.30), cancer (aOR= 25.80, 95% CI=1.60 -409.40) and gouty arthritis (aOR= 8.80, 95%CI= 1.20-59.60) was also associated with the group at risk of malnutrition. In addition, the protective effect of exercise was associated with malnutrition and risk of malnutrition, respectively (aOR=0.04, 0.13, 95%CI=0.00-0.80, 0.00-0.50).

Discussion

Although the prevalence of malnutrition among the elderly identified in this study agreed with a related study of hospitalized elderly patients,[23] i.e., 4.4% and 6.1%, respectively, the total population was limited and did not include bedridden and other patients unable to visit hospitals which could have affected the accuracy of malnutrition prevalence. The prevalence of the at risk of malnutrition group was 18.7%. However, in this study, the prevalence was lower in both malnutrition and at risk of malnutrition groups compared with the that of participants in tertiary care hospitals, which were more complex than those in community hospitals.[1]

Table 1. Demographic characteristics of elderly patients at an outpatient clinic, community hospital in Thailand

Characteristic	Total	Nutritional status assessed by MNA® Overall risk of malnutrition (N = 21)		*p*-value
		Malnutrition	At risk of Malnutrition	
	N = 91	N = 4	N = 17	
	N (%)	N (%)	N (%)	
Sex				0.112
Male	37 (40.66)	0 (0.00)	5 (13.51)	
Female	54 (59.34)	4 (7.41)	12 (22.22)	
Age (years)				0.262
Mean ± SD	70.54 ± 6.89	67.50 ± 8.06	72.24 ± 7.31	
Min - Max	60 - 94	61 - 79	62 - 88	
60-69	46 (50.55)	3 (6.52)	7 (15.22)	
70-79	36 (39.56)	1 (2.78)	6 (16.67)	
≥80	9 (9.89)	0 (0.00)	4 (44.44)	
Nationality				0.859
Thai	90 (98.90)	4 (4.44)	17 (18.89)	
NonThai	1 (1.10)	0 (0.00)	0 (0.00)	
Health coverage scheme				0.662
Universal Health coverage	78 (85.71)	4 (5.13)	14 (17.95)	
Civil Servant Medical Benefit Scheme	13 (14.29)	0 (0.00)	3 (23.08)	
Religion				0.736
Buddhist	89 (97.80)	4 (4.49)	17 (19.1)	
Other	2 (2.20)	0 (0.00)	0 (0.00)	
Occupation				0.209
Unemployed	54 (59.34)	3 (5.56)	14 (25.93)	

Table 1. Demographic characteristics of elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Total	Nutritional status assessed by MNA® Overall risk of malnutrition (N = 21)		*p*-value
		Malnutrition	At risk of Malnutrition	
	N = 91	N = 4	N = 17	
	N (%)	N (%)	N (%)	
Agriculture	23 (25.27)	0 (0.00)	1 (4.35)	
Employee	11 (12.09)	1 (9.09)	1 (9.09)	
Merchant or personal business	3 (3.30)	0 (0.00)	1 (33.33)	
Education level				0.808
Illiterate	2 (2.20)	0 (0.00)	1 (50.00)	
Primary school	74 (81.32)	4 (5.41)	15 (20.27)	
Secondary school	7 (7.69)	0 (0.00)	1 (14.29)	
Vocational degree	5 (5.49)	0 (0.00)	0 (0.00)	
Bachelor's degree	3 (3.3)	0 (0.00)	0 (0.00)	
Monthly family income (THB)				0.064
≤1000	18 (19.78)	3 (16.67)	3 (16.67)	
1001-5000	36 (39.56)	1 (2.78)	8 (22.22)	
≥ 5001	37 (40.66)	0 (0.00)	6 (16.22)	
Smoking history				0.53
No	10 (10.99)	1 (10.00)	1 (10.00)	
Yes	81 (89.01)	3 (3.70)	16 (19.75)	
Alcohol consumption history				0.707
No	8 (8.79)	0 (0.00)	1 (12.50)	
Yes	83 (91.21)	4 (4.82)	16 (19.28)	

Table 1. Demographic characteristics of elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Total	Nutritional status assessed by MNA® Overall risk of malnutrition (N = 21)		*p*-value
		Malnutrition	At risk of Malnutrition	
	N = 91	N = 4	N = 17	
	N (%)	N (%)	N (%)	
BMI (kg/m²)				0.039
Mean ± SD	24.68 ± 4.28	18.39 ± 0.81	24.18 ± 4.03	
Min - Max	15.57 - 39.29	17.60 - 19.15	15.57 - 32.05	
<18.50 (Underweight)	6 (6.59)	2 (33.33)	1 (16.67)	
18.50-22.90 (Normal weight)	26 (28.57)	2 (7.69)	6 (23.08)	
23.00-24.90 (Overweight)	22 (24.18)	0 (0.00)	4 (18.18)	
25.00-29.90 (Pre-obesity)	27 (29.67)	0 (0.00)	4 (14.81)	
≥30.00 (Obesity)	10 (10.99)	0 (0.00)	2 (20.00)	
Comorbidity				
Hypertension	60 (65.93)	3 (5.00)	14 (23.33)	0.244
Dyslipidemia	58 (63.74)	3 (5.17)	11 (18.97)	0.883
Diabetes mellitus	32 (35.16)	1 (3.13)	6 (18.75)	0.909
Chronic kidney disease	11 (12.09)	0 (0.00)	5 (45.45)	0.046*
Heart disease	9 (9.89)	0 (0.00)	1 (11.11)	0.628
Gouty arthritis	8 (8.79)	0 (0.00)	4 (50.00)	0.055
COPD	7 (7.69)	0 (0.00)	2 (28.57)	0.684
Thyroid disorder	5 (5.49)	0 (0.00)	2 (40.00)	0.424
Allergy/asthma	4 (4.40)	0 (0.00)	2 (50.00)	0.25
All types of cancer history	4 (4.40)	0 (0.00)	3 (75.00)	0.013*
Disability	2 (2.20)	0 (0.00)	0 (0.00)	0.736
Thalassemia/anemia	2 (2.20)	0 (0.00)	2 (100.00)	0.012*

Table 1. Demographic characteristics of elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Total	Nutritional status assessed by MNA® Overall risk of malnutrition (N = 21)		*p*-value
		Malnutrition	At risk of Malnutrition	
	N = 91	N = 4	N = 17	
	N (%)	N (%)	N (%)	
History of COVID-19				0.009*
No	83 (91.21)	2 (2.41)	15 (18.07)	
Yes	8 (8.79)	2 (25.00)	2 (25.00)	
Medication affecting appetite loss				
Statins	6 (6.59)	0 (0.00)	2 (33.33)	0.575
Heart failure medication	15 (16.48)	0 (0.00)	4 (26.67)	0.489
Tricyclic Antidepressants	5 (5.49)	1 (20.00)	3 (60.00)	0.007*

SD; Standard deviation, BMI; Body mass index, kg/m²; kilogram per meter square, COPD; Chronic Obstructive Pulmonary Disease

[a]Level of significant: *$p < 0.05$

Table 2. Prevalence of nutritional status among elderly patients at an outpatient clinic, community hospital in Thailand

Characteristic	N (%)	95%CI
At risk of malnutrition	17 (18.70)	0.11 to 0.28
Malnutrition	4 (4.40)	0.01 to 0.11

CI= confident inte

Table 3. Univariable and multivariable binary logistic regression analysis to assess relationships between associated factors and overall risk of malnutrition among elderly patients at an outpatient clinic, community hospital in Thailand

Characteristic	Nutritional status assessed by MNA®		Crude ORs (95% CI)	Adjusted ORs (95% CI)
	Normal nutrition N = 70 N (%)	Overall risk of malnutrition N = 21 N (%)		
Sex				
Male	32 (86.50)	5 (13.50)	1	
Female	38 (70.40)	16 (29.60)	2.70 (0.80-8.10)	
Age (years)				
Mean ± SD	70.00 ± 7.00	71.00 ± 7.00	1.02 (0.90-1.00)	
<70	36 (78.30)	10 (21.70)	1	
≥70	34 (75.60)	11 (24.40)	1.20 (0.40-3.00)	
Monthly family income (THB)				
≤1000	12 (66.70)	6 (33.30)	2.60 (0.60-9.60)	
1001-5000	27 (75.00)	9 (25.00)	1.70 (0.50-5.40)	
≥5001	31 (83.80)	6 (16.20)	1	
Living				
Living alone	7 (70.00)	3 (30.00)	1.50 (0.30-6.30)	
Living with family	63 (77.80)	18 (22.20)	1	
Eating habit in the past 3 months				
Homemade	64 (77.10)	19 (22.90)	0.90 (0.10-4.70)	
Purchased	6 (75.00)	2 (25.00)	1	
Nutrition supplements				
No	52 (76.50)	16 (23.50)	1	
Yes	18 (78.30)	5 (21.70)	0.90 (0.20-2.80)	

Table 3. Univariable and multivariable binary logistic regression analysis to assess relationships between associated factors and overall risk of malnutrition among elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Nutritional status assessed by MNA®		Crude ORs (95% CI)	Adjusted ORs (95% CI)
	Normal nutrition N = 70 N (%)	Overall risk of malnutrition N = 21 N (%)		
Exercise				
No	19 (57.60)	14 (42.40)	1	1
Yes	51 (87.90)	7 (12.10)	0.20** (0.00-0.50)	0.10** (0.00-0.40)
Duration of exercise				
<30 minutes/day	14 (73.70)	5 (26.30)	1	
≥30 minutes/day	34 (94.40)	2 (5.60)	0.17* (0.00-0.90)	
Smoking history				
No	62 (76.50)	19 (23.50)	1	
Yes	8 (80.00)	2 (20.00)	0.80 (0.10-4.10)	
Alcohol consumption history				
No	63 (75.90)	20 (24.10)	1	
Yes	7 (87.50)	1 (12.50)	0.50 (0.00-3.80)	
History of falls in the previous year				
No	64 (77.10)	19 (22.90)	1	
Yes	6 (75.00)	2 (25.00)	1.10 (0.20-6.00)	
Allergy/asthma				
No	68 (78.20)	19 (21.80)	1	
Yes	2 (50.00)	2 (50.00)	3.60 (0.40-27.10)	
Gouty arthritis				
No	66 (79.50)	17 (20.50)	1	1
Yes	4 (50.00)	4 (50.00)	3.90 (0.80-17.10)	4.20 (0.50-33.30)

Table 3. Univariable and multivariable binary logistic regression analysis to assess relationships between associated factors and overall risk of malnutrition among elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Nutritional status assessed by MNA®		Crude ORs (95% CI)	Adjusted ORs (95% CI)
	Normal nutrition N = 70 N (%)	Overall risk of malnutrition N = 21 N (%)		
Diabetes mellitus				
No	45 (76.30)	14 (23.70)	1	
Yes	25 (78.10)	7 (21.90)	0.90 (0.30-2.50)	
Dyslipidemia				
No	26 (78.80)	7 (21.20)	1	
Yes	44 (75.90)	14 (24.10)	1.20 (0.40-3.30)	
Hypertension				
No	27 (87.10)	4 (12.90)	1	
Yes	43 (71.70)	17 (28.30)	2.70 (0.80-8.70)	
Chronic kidney disease				
No	64 (80.00)	16 (20.00)	1	1
Yes	6 (54.50)	5 (45.50)	3.30 (0.90-12.30)	2.10 (0.30-12.90)
All types of cancer history				
No	69 (79.30)	18 (20.70)	1	1
Yes	1 (25.00)	3 (75.00)	11.50* (1.10-117.20)	27.50* (1.40-521.60)
COPD				
No	65 (77.40)	19 (22.60)	1	
Yes	5 (71.40)	2 (28.60)	1.30 (0.20-7.60)	
Heart disease				
No	62 (75.60)	20 (24.40)	1	
Yes	8 (88.90)	1 (11.10)	0.40 (0.00-3.20)	

Table 3. Univariable and multivariable binary logistic regression analysis to assess relationships between associated factors and overall risk of malnutrition among elderly patients at an outpatient clinic, community hospital in Thailand (Cont.)

Characteristic	Nutritional status assessed by MNA®		Crude ORs (95% CI)	Adjusted ORs (95% CI)
	Normal nutrition N = 70 N (%)	Overall risk of malnutrition N = 21 N (%)		
Thyroid disorder				
No	67 (77.90)	19 (22.10)	1	
Yes	3 (60.00)	2 (40.00)	2.40 (0.30-15.10)	
History of COVID-19				
No	66 (79.50)	17 (20.50)	1	1
Yes	4 (50.00)	4 (50.00)	3.90 (0.80-17.10)	14.30* (1.90-106.80)
Statins (atorvastatin)				
No	66 (77.60)	19 (22.40)	1	
Yes	4 (66.70)	2 (33.30)	1.70 (0.20-10.20)	
Heart failure medication (ACEI)				
No	59 (77.60)	17 (22.40)	1	
Yes	11 (73.30)	4 (26.70)	1.30 (0.30-4.40)	
Tricyclic Antidepressants				
No	69 (80.20)	17 (19.80)	1	1
Yes	1 (20.00)	4 (80.00)	16.20* (1.70-154.70)	11.30 (0.50-235.30)

COPD; Chronic Obstructive Pulmonary Disease, ACEI; Angiotensin-converting-enzyme inhibitors, MNA®; Mini Nutritional Assessment®, ORs; odds ratio, CI; confident interval, SD; Standard deviation

Level of significant: $^{**}p < 0.01$, $^{*}p < 0.05$

Multivariable binary logistic regression analysis (Enter): adjusted for exercise, gouty arthritis, chronic kidney disease, all types of cancer history, history of COVID-19, tricyclic antidepressants

Table 4. Univariable and multivariable multinomial logistic regression analysis of potentially associated factors of malnutrition and at risk of malnutrition among elderly patients at an outpatient clinic, community hospital in Thailand

Variable	Malnutrition Versus Normal nutrition				At risk of Malnutrition Versus Normal nutrition			
	Crude		Adjust-		Crude		Adjusted	
	ORs	95% CI	ed ORs	95% CI	ORs	95% CI	ORs	95% CI
Exercise								
No	1		1		1		1	
Yes	0.10	0.00-1.20	0.04*	0.00-0.80	0.20**	0.00-0.60	0.13**	0.00-0.50
Gouty arthritis								
No	NA				1		1	
Yes					5.10*	1.10-22.90	8.80*	1.20-59.60
All types of cancer history								
No	NA				1		1	
Yes					14.80*	1.40-152.70	25.80*	1.60-409.40
History of COVID-19								
No	1		1		1		1	
Yes	16.50*	1.80-149.50	55.00**	2.70-1110.30	2.20	0.30-13.10	7.60	0.90-62.00

NA; cannot be analyzed due to lacking an event in malnutrition and/or at risk of malnutrition and/or normal nutrition group

ORs; odds ratio, CI; confident interval

Level of significant: $^{**}p < 0.01$, $^{*}p < .05$

Pseudo R^2: 0.29

Log Likelihood: Chi-Square 30.69, df 8, p<0.001

In addition, after adjusting for confounding variables, the results indicated that patients who exercised were adversely associated with malnutrition and at risk of malnutrition. This occurred due to the adaptation processes induced by exercise, leading to total and peripheral nitrogen storage and enhanced muscle anabolism among the elderly.[24, 25] Regular exercise, especially the resistance training program, promotes muscle anabolism and protein metabolism and decreases sarcopenia and malnutrition risk.[26] muscle strength, and muscle performance in older people with sarcopenia. Methods: All randomized controlled trials on the effects of resistance training on outcome variables in older people with sarcopenia were searched on Pubmed, Embase, Cochrane Library, the China National Knowledge Infrastructure (CNKI This intervention should be implemented in public health policy to encourage elderly patients to participate in regular resistance exercise regimens.

Cancer and gouty arthritis were both positively associated with malnutrition. A relationship between serum albumin and nutritional status could explain the strong association between gout and malnutrition. Serum albumin levels may indicate protein-losing disorders, dietary deficiency or systemic inflammation. For each 1 g/L of lower serum albumin, the likelihood of gout increased by 9%, which could be explained by ongoing systemic inflammation.[27] side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. In inflammatory states, cell capillary permeability was increased, resulting in albumin flux into cells and a heightened oxidation and scavenging process. In addition, albumin functions as an intracellular amino acid donor for cell proliferation, which was significantly more prevalent in inflammatory states. Consequently, albumin degradation was greater in inflammatory states than in normal states, resulting in decreased albumin mass despite the possibility of increased albumin synthesis during the inflammatory process.[28, 29] side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc.

However, the associations between cancer and malnutrition could have been caused by multiple factors including illness symptoms such as nausea, vomiting, anorexia and dysphagia[30] side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. and side effects from chemotherapy or radiation and gastro-intestinal obstruction.[31]side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. Hence, elderly individuals with cancer and gouty arthritis require closer dietary monitoring; therefore, consulting a nutritionist is recommended.

The relationship between the history of COVID-19 and malnutrition necessitated a discussion of four areas. Initially, the virus entered the host's body using an angiotensin-converting enzyme 2 receptors, typically located in the lungs and gastrointestinal system. Due to the abundance of these receptors in the gastrointestinal system, they have become one of the primary targets of SARS-CoV-2.[32, 33] side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/

or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. Thus, in addition to respiratory symptoms, the elderly with a history of COVID-19 exhibit severe digestive system symptoms. Second, COVID-19 increases the production of acute-phase proteins during an acute inflammatory response, requiring the consumption of albumin and muscle protein.(34)side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. Subsequently, COVID-19 caused symptoms such as anxiety and loss of appetite, which may eventually lead to malnutrition. (35) side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. Lastly, malnutrition can increase the likelihood of COVID-19 by reducing T- and B-cell production due to lymphoid organ atrophy.(36) side effects of anticancer therapies can also lead to inadequate nutrient intake and subsequent malnutrition. The nutritional screening aims to identify patients at risk of malnutrition for prompt treatment and/or careful follow-up. Methods and results: This manuscript highlights the need of an interdisciplinary approach (oncologist, nutritionist, dietitian, psychologist, etc. Nonetheless, malnutrition may alter innate and adaptive immune responses, increasing susceptibility to COVID-19. The reduced T-cell response was caused by structural and functional thymic involution. All complement components (except C4) are diminished in emaciated patients, particularly C3 and factor B. In addition, malnutrition impairs phagocytic function and the production of cytokines and antibodies.[37] caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 Malnutrition might thus have an impact on those prone to COVID-19. Therefore, patients with COVID-19 should be assessed for malnutrition and given treatment as soon as possible in both nutritional status and COVID-19 treatment to prevent further morbidity and mortality.

This study encountered limitations. The number of patients was comparatively low, resulting in minuscule totals in each category. Due to the small sample size, the confidence interval for the estimated odds ratio was relatively wide. Additionally, the present study was conducted in a single hospital; the data may not be generalizable to the entire country, but they may reflect the situation of malnutrition and the risk of malnutrition patients in community hospitals in Thailand.

Conclusion

Malnutrition constitutes a devastating condition with several comorbidities among the elderly posing a significant worldwide public health problem. The history of COVID-19 and physical activity were associated with malnutrition, whereas cancer, gouty arthritis and physical activity were associated with those at risk for malnutrition. In addition, residing in a community hospital may indicate a lack of access to health literacy; therefore, the Ministry of Public Health and healthcare providers should develop comprehensive guidelines and strategies to screen and prevent malnutrition among the elderly as one of the standard healthcare systems and educate themselves on malnutrition and its complications.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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RELIABILITY, VALIDITY AND AGREEMENT OF THE THAI SELF-REPORTED FIBROMYALGIA SURVEY QUESTIONNAIRE AMONG PATIENTS WITH CHRONIC MUSCULOSKELETAL PAIN

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Abstract

Background: Fibromyalgia (FM) diagnosis is typically based on the American College of Rheumatology (ACR) criteria, relying on patient-reported symptoms. The Thai self-reported Fibromyalgia Survey Questionnaire (FSQ) was developed based on the 2016 version of the ACR criteria set.

Objectives: This study aimed to evaluate the internal consistency, convergent validity and agreement of the self-reported FSQ compared with the telephone interview of a physician among patients with chronic musculoskeletal pain.

Methods: The Thai FSQ consisting of 25 questions: 19 for widespread pain index (WPI) and 6 for symptom severity scale (SSS), was developed by three Thai physiatrists. The fibromyalgia severity (FS) scale (the sum of WPI and SSS: 0-31) of 13 or more was used to diagnose fibromyalgia. All participants completed a self-reported paper research questionnaire in a private room. Then 24-48 hours later, participants underwent a telephone interview with the Thai FSQ. The internal consistency and convergent validity of the Thai self-reported FSQ were assessed using Cronbach's alpha and Pearson's correlation, respectively. The agreement between the Thai self-reported FSQ (FS scale ≥13) and the telephone interview using the 2016 ACR criteria for diagnosing fibromyalgia was evaluated using Cohen's kappa.

Results: Of 89 participants, the majority were females (66.3%) with a mean age of 53.5±15.9 years and had an educational level of bachelor's degree or higher (79.7%). Cronbach's alpha was 0.82, while the correlation between the FS scale and EQ-5D-5L utility was -0.48 (p <0.001). Cohen's kappa for diagnosis agreement was 0.55 (p < 0.001).

Conclusion: The Thai self-reported FSQ exhibited good internal consistency and moderate construct validity. The diagnostic agreement of the Thai self-reported FSQ with the telephone interview was moderate. Although this questionnaire could be used as a screening tool, physicians would need to confirm the diagnosis of fibromyalgia.

Keywords: Fibromyalgia, Questionnaire, Reliability, Validity, Agreement

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Introduction

Fibromyalgia (FM) is characterized by widespread chronic pain, general hypersensitivity, insomnia, fatigue, cognitive problems, anxiety and depression.[1] The prevalence of FM varies depending on the definition and criteria used for diagnosis, as well as the demographic characteristics of the population studied. The study of Prateepavanich et al. in Thailand reported that the prevalence of FM was 25.7% among 70 patients with chronic myofascial pain syndrome.[2] The etiology of FM is not clearly understood; however, current scientific evidence suggests that nociceptive alterations including central and peripheral sensitization and a reduction in endogenous pain inhibitory signals may contribute to the pathophysiology of FM.[3] Diagnosing FM remains a challenge due to the absence of specific laboratory or imaging tests. As a result, diagnosis is primarily based on clinical symptoms.

Fibromyalgia (FM) diagnosis is typically based on the American College of Rheumatology (ACR) criteria, which have evolved over time. The 2010 version of the ACR criteria included two components: the Widespread Pain Index (WPI), assessing the number of pain sites (range 0 to 19), and the Symptom Severity Scale (SSS) score (range 0 to 12). FM was diagnosed when the following three criteria were met: (1) a WPI ≥7 and an SSS score ≥5 or a WPI of 3-6 plus an SSS score ≥9; (2) the symptoms had been present for at least three months and (3) the symptoms were not attributable to other diseases.[1] In 2011, the ACR criteria were revised to include the number of symptoms present during the last six months including headache, lower abdominal cramps or pain and depression, instead of general somatic symptoms. In addition, the Fibromyalgia Severity (FS) scale, the sum of the WPI and SSS, was introduced for FM diagnosis when it reached ≥13.[4] Most recently, the 2016 version of the ACR diagnostic criteria added generalized pain, defined as pain in at least four of five regions (axial, right/left upper extremities and right/left lower extremities), to the diagnostic criteria.[5]

The ACR diagnosis for FM relies on patient-reported symptoms. Given that the ACR criteria do not require physical examinations; thus, the patient could self-assess their symptoms for a potential diagnosis of FM. Regarding this, several countries such as Iran, German, Brazil and Italy have developed self-reported fibromyalgia survey questionnaires (FSQ) in their language.[6-9] Currently, the FSQ is unavailable in Thai. Therefore, the present study aimed to develop a Thai version of the self-reported FSQ and to evaluate its internal consistency and construct validity. Furthermore, agreement for FM diagnosis between the Thai self-reported FSQ and telephone interview by a physician was assessed.

Methods

Study design and participants

This cross-sectional study was approved by the Institutional Review Board of the Royal Thai Army Medical Department (IRB number: R155h/64). Eligible participants were enrolled prospectively at the Department of Rehabilitation Medicine, Phramongkutklao Hospital in Bangkok, Thailand, from March 2022 to October 2022. All participants were informed, and written consent was obtained before participating in this study. Eligible criteria included patients with chronic musculoskeletal pain aged at least 20 years. Patients who could not read questionnaires due to illiteracy or visual impairments, those who were pregnant, and those with psychiatric disorders were excluded.

Questionnaire

The Thai FSQ was developed by three Thai physiatrists with five to ten years of experience diagnosing fibromyalgia and had upper-intermediate English skills (IELTS score of 6.5 or equivalent). The development of the Thai FSQ was based on discussions among the three physiatrists on how they interview patients to diagnose FM in their clinical practice using the 2016 ACR criteria.

The research questionnaire consists of four parts: (1) general information, (2) Thai FSQ consisting of 19 questions for WPI and six questions for SSS (**Supplementary Material**), (3) understanding of the Thai FSQ using the

5-likert scale (**Table 1**) and (4) Thai EQ-5D-5L to calculate health utility ranging from 0 (the worst) to 1 (the best).[10] The survey consisted of two stages: first, participants completed a self-administered paper research questionnaire in a private room. The second stage occurred 24 to 48 hours later, wherein participants joined a telephone interview with the Thai FSQ.

Statistical analysis

The sample size was calculated based on a power of 0.90, and the probability of type I error was set at 0.05. The number of items or raters (k) = 26. The value of Cronbach's alpha at null hypothesis (CA0) = 0.5, and the expected value of Cronbach's alpha (CA1) = 0.7. The internal consistency of the Thai SEQ was evaluated using Cronbach's alpha. Construct (convergent) validity was determined using Pearson's correlations between the sum of the WPI+SSS, known as the Fibromyalgia severity (FS) scale and the health utility of EQ-5D-5L. The diagnostic agreement between the Thai FSQ (FS scale ≥13) and the telephone interview of a physician (the 2016 ACR criteria) was evaluated using Cohen's kappa. A *p*-value less than 0.05 was considered statistically significant. Additionally, the sensitivity and specificity of Thai FSQ for FM diagnosis were calculated using the physician's telephone interview as the gold standard.

Results

Eighty-nine eligible patients (30 males and 59 females) participated in this study. As shown in Table 1, the mean age of the participants was 53.5 ± 15.9 years. For educational levels, 79.7% had bachelor's degrees or higher. Approximately 87% had almost entirely or an entire understanding of the Thai FSQ. The overall Cronbach's alpha of the Thai FSQ was 0.82, indicating good internal consistency. Convergent validity calculated by Pearson's correlations showed a moderate negative correlation between the FS scale and the health utility of EQ-5D-5L (r = -0.48, $p < 0.001$) **(Figure 1)**. The agreement on the diagnosis of fibromyalgia between self-administration and telephone interview by a physician revealed moderate agreement (Percent agreement 83.2%, Cohen's kappa=0.55, $p < 0.001$). Based on the physician telephone interview, 22.5% (95% confidence interval [CI]: 14.3% to 32.5%) received a diagnosis of FM. The sensitivity and specificity of the Thai FSQ were 75% (95%CI: 50.9% to 91.3%) and 85.5% (95%CI: 75% to 92.8%), respectively, as reported in **Table 2**.

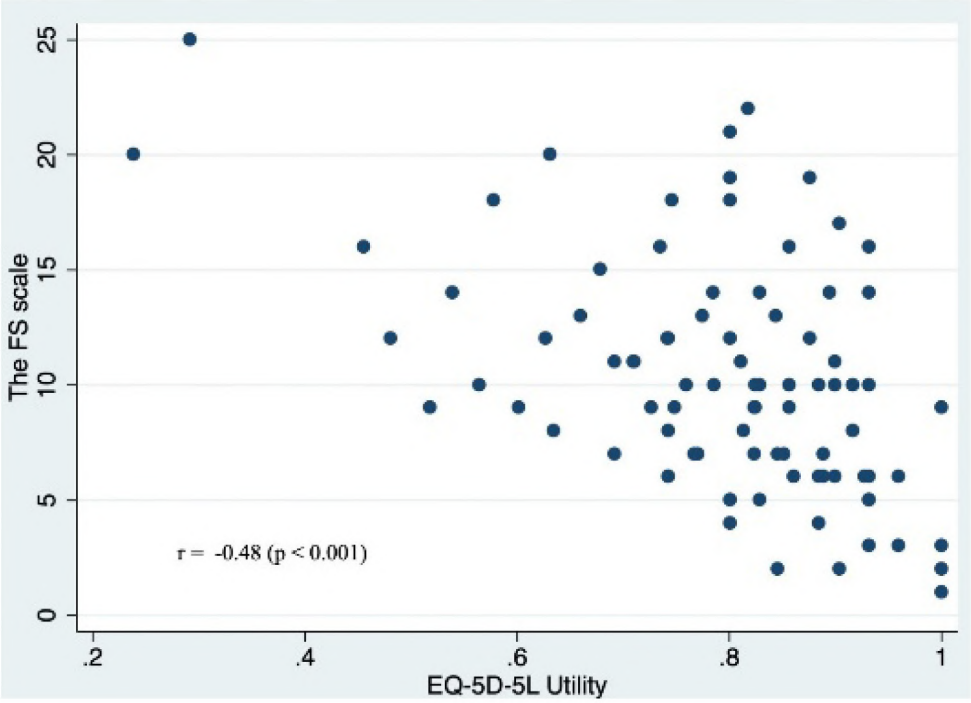

Figure 1. Pearson's correlations between the FS and health utility of EQ-5D-5L

Table 1. Demographic data of participants

Characteristics	
Sex, Female[2]	56 (63%)
Age (years)[1]	53.5 (15.9)
Educational level[2]	
Higher than bachelor's or equivalent	22 (24.7%)
Bachelor's or equivalent	49 (55%)
Secondary	14 (15.7%)
Primary	2 (2.3%)
Pre-primary	2 (2.3%)
Understanding of the Thai FSQ[2]	
Completely understand	61 (68.5%)
Almost completely understand	16 (18%)
Partially understand	10 (11.2%)
Almost completely do not understand	1 (1.1%)
Completely do not understand	1 (1.1%)

[1] Mean (SD), [2] number (%)

Table 2. Agreement of the FM diagnosis between self-administration and telephone interview

FS scale ≥ 13 (Self-administration)	ACR 2016 diagnostic criteria (Telephone interview)		Total
	Yes	No	
Yes	15 (60%, 75%)	10 (40%, 14.5%)	25 (100%, 28.1%)
No	5 (7.8%, 25%)	59 (92.2%, 85.5%)	64 (100%, 71.9%)
Total	20 (22.5%, 100%)	69 (77.5%, 100%)	89 (100%, 100%)

Values are presented as number (row percentage, column percentage)
FM: Fibromyalgia; ACR: American college of rheumatology; FS: Fibromyalgia severity

Discussion

To our knowledge, this study was the first to develop the FSQ in Thai version. The results showed that the Thai FSQ exhibited good internal consistency. The overall Cronbach alpha of Thai FSQ was 0.82, which was slightly higher than the German (0.71), Brazilian (0.74), and Italian (0.71) Versions.[7-9] The convergent validity of Thai FSQ with EQ-5D-5L utility was moderate (r = -0.48, p<0.001), similar to the German Version that showed a moderate degree of convergent construct validity with PHQ-4 (r = 0.48, p <0.001).[8] Furthermore, the diagnosis agreement for FM of the Thai FSQ with the telephone interview was moderate, with Cohen's kappa=0.55, which was lower than the Italian Version, Cohen's kappa=0.65.[9] One possible explanation was that the present study used different diagnosis criteria between the Thai FSQ (FS scale ≥13) and the physician telephone interview (2016 ACR criteria).

Additionally, based on the 2011 ACR criteria, the FS scale ≥13 showed a sensitivity of 96.6% and a specificity of 91.8% in the diagnosis of FM.[4] The present study found that the FS scale ≥13 revealed a lower sensitivity and specificity

when the 2016 ACR criteria were used as a gold standard for diagnosing FM. This might have been due to the addition of generalized pain in the diagnostic criteria of the 2016 Version.

Several limitations should be considered when interpreting the findings of this study. First, no other specialists with experience in FM diagnosis such as rheumatologists participated or collaborated in developing the Thai FSQ. Second, most participants in this study had attained a high level of education (bachelor's degree or higher), potentially limiting the generalizability of the results to individuals with lower educational backgrounds. The present study was conducted solely in Bangkok, Thailand's capital; thus, the findings may only represent part of the country. Moreover, the sample size was not estimated to determine the diagnostic properties of the Thai FSQ, which may have implications regarding the precision of the results. Lastly, the test-retest reliability of the Thai FSQ was not assessed in this study.

Conclusion

The Thai FSQ showed good internal consistency, moderate construct validity and moderate agreement with the diagnosis of physicians. Therefore, the Thai FSQ may be used as a primary survey to evaluate fibromyalgia among patients with chronic pain.

Supplemental material

Supplemental material for this article is available online.

Disclosure

The authors have no conflicts of interest to declare.

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UNUSUAL PRESENTATION OF MALIGNANT THYMOMA ASSOCIATED NEPHROTIC SYNDROME WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS: A CASE REPORT

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Abstract

Paraneoplastic syndromes (PS) are the consequences of hormones or immune cross-reactivity produced by a tumor. Nephrotic syndrome (NS) is an extremely rare PS resulting from a thymoma. Here, the case of a 55-year-old woman presenting progressive generalized edema and foamy urine is reported. The patient's chest CT scan showed anterior mediastinum with intramural punctate calcification size 8.6x7.0x10.2 cm. The case was reviewed at the multi-dispensary team conference, and the clinical diagnosis was an unusual presentation of malignant thymoma known as NS. After that, a thymectomy and kidney biopsy was performed. Histopathologic examination showed Thymoma type B and focal segmental glomerulosclerosis, respectively. Therefore, we considered it paraneoplastic nephrotic syndrome (PNS), without glucocorticoids, immunosuppressants or other drugs to treat NS. After the thymectomy, her clinical spontaneous resolved at the first follow-up, proposing a causative relationship between the two conditions.

Keywords: Malignant thymoma-associated nephrotic syndrome, Paraneoplastic nephrotic syndrome

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Introduction

Undoubtedly, one-third of the patients with thymoma also present paraneoplastic syndrome. Those manifestations are the effects of hormones or immune cross-reactivity produced by malignancy. The most common condition of those manifestations is myasthenia gravis (MG). Other associated autoimmune disorders include thymoma-associated multiorgan autoimmunity, pure red cell aplasia, etc.[1] However, nephrotic syndrome (NS) is extremely rare, resulting from a thymoma. This clinical syndrome includes nephrotic range proteinuria (24-hour urine protein>3 g/24 hours), hypoalbuminemia (serum albumin <2.5 g/dL), generalized edema, and hyperlipidemia (total cholesterol >350 mg/dL).[2] In the related reports of paraneoplastic nephrotic syndrome (PNS), almost all (80% of cases) of glomerular lesions involve minimal change disease or membranous glomerulonephritis.[3-10]

Moreover, focal segmental glomerulosclerosis (FSGS) is a type of kidney disease characterized by scarring or sclerosis in specific areas (segments) of the kidneys' filtering units called glomeruli, one of the leading causes of NS among children and adults. However, the relationship between the two conditions as PNS of thymoma is scarce. Here, we present a case report of NS associated with thymoma, kidney biopsy-proven FSGS, and clinical improvement after performing a thymectomy.

A case report

A 55-year-old female was referred to an Internal Medicine Inpatient Department for a consultation based on suspicion of NS. The patient reported the onset of progressive generalized edema and foamy urine for two weeks. Her family history showed no particular diseases, and she was physically fit in the past. Her physical examination showed that she had eyelid edema and pitting edema in both legs and arms. She attended a primary care hospital for a workup. The laboratory data at admission are shown in **Table 1.** The following symptoms were associated with this case: albuminuria, hyperlipidemia, edema and hypoalbuminemia. These clinical findings are consistent with the diagnosis of NS.

Unfortunately, initial chest x-ray images showed a heterogeneous well-circumscribed mass

Table 1. Laboratory data

Variable	At admission	After thymectomy
Blood urea nitrogen (BUN) (mg/dL)	31	10
Creatinine (Cr) (mg/dL)	1.59	1.03
Albumin (g/dL)	1.4	1.7
Globulin (g/dL)	2.5	3.2
Total cholesterol (mg/dL)	619	
Urine protein 24 hours --g/24 hours	5.3	
urine protein creatinine ratio (UPCR) (g/g Cr)	4.6	1.4
Urine analysis		
- Urine protein	3+	
- Urine red blood cells (cells/HPF)	3-5 (no dysmorphic RBC)	
- Urine white blood cells (cells/HPF)	5-10	
HBsAg, Anti-HCV, Anti-HIV	negative	
Antinuclear antibody (ANA)	Positive 1:80	
Beta-human chorionic gonadotropin (beta-HCG) (MU/ml)	1.31	
Alpha-fetoprotein (ng/ml)	2.75	

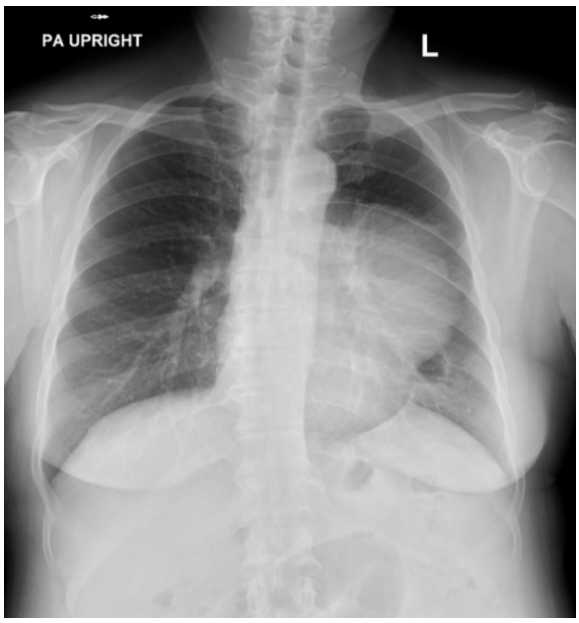

Figure 1. Chest x-ray images showed a heterogeneous well-circumscribed mass at the left upper lung, of which the silhouette lay on the left heart border with an obtuse angle. The estimated diameter from the chest X-ray was 10.3 cm.

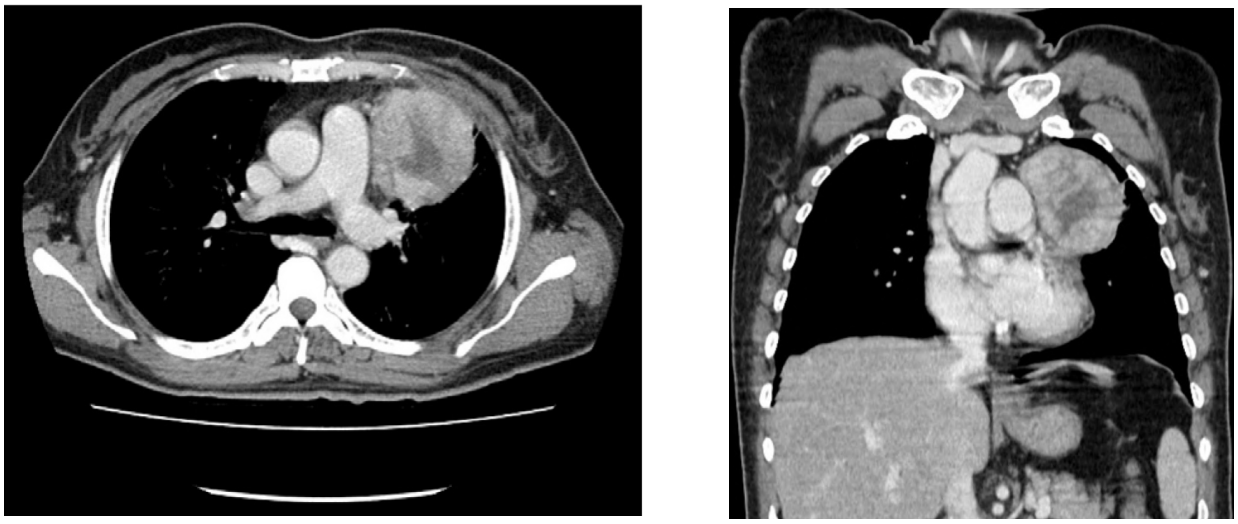

Figure 2. CT chest with the whole abdomen showed the lobular shape of heterogeneously enhancing necrotic mass at the left-sided anterior mediastinum with intramural punctate calcification size 8.6x7.0x10.2 cm

at the left upper lung, of which the silhouette lay on the left heart border with an obtuse angle. The estimated diameter from the chest X-ray was 10.3 cm **(Figure 1).** Then she underwent a computerized tomography (CT) scan of the chest including the whole abdomen, to work up the mediastinal mass. The CT chest with the whole abdomen showed the lobular shape of heterogeneously enhancing necrotic mass at the left-sided anterior mediastinum with intramural punctate calcification size 8.6x7.0x10.2 cm **(Figure 2).** No obviously observed uterine mass, lungs, liver, or bone metastasis was shown. Her clinical data and CT scan were reviewed during a multidisciplinary team conference, and the consensus summary concluded an NS was associated with a thymic tumor. Finally, she underwent a thymectomy for total tumor removal. A kidney biopsy was performed for a further workup to determine the cause of NS. The kidney biopsy suggested FSGS **(Figure 3)** and immunofluorescence microscopy findings. All

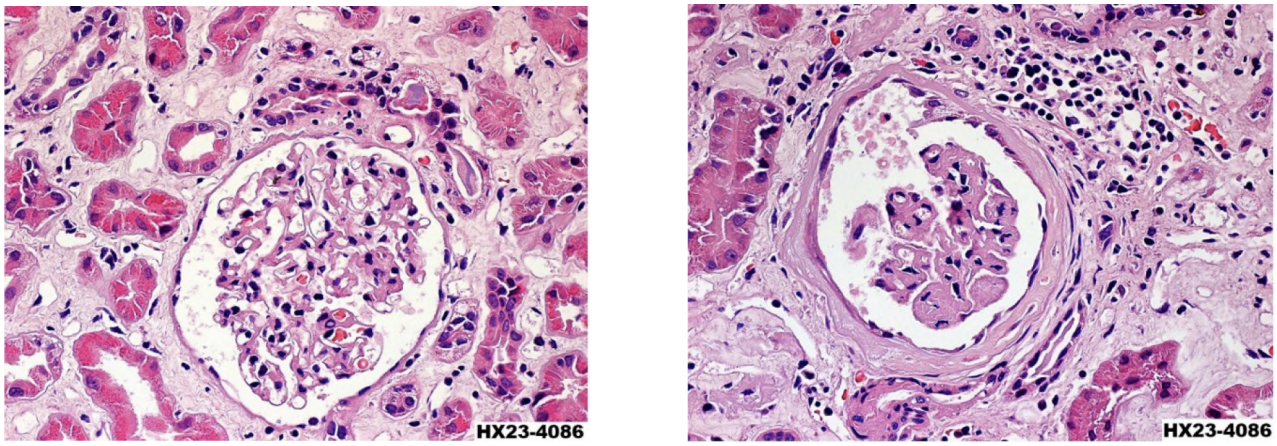

Figure 3. Light microscopy findings of the kidney biopsy identified seven glomeruli. Six glomeruli showed mild expansion of some mesangial areas with no definite change in the thickness of the capillary wall. One glomerulus with periglomerular fibrosis showed mesangial sclerosis. Interstitial edema and mild diffuse with focal dense lymphomonocytic infiltrate were observed. No vasculopathy was present. Immunofluorescence microscopy findings: all nine glomeruli in each frozen section showed no immune complex deposition.

nine glomeruli in each frozen section showed no deposition of the immune complex. Unfortunately, electron microscopy was unavailable to diagnose and evaluate the FSGS. The thymectomy pathology results showed a thymic epithelial tumor, consistent with thymoma type B **(Figures 4 and 5).**

We diagnosed it as PNS without glucocorticoids, immunosuppressants or other drugs used to treat the NS. After the thymectomy, the first follow-up on her urine protein creatinine ratio (UPCR) at the outpatient unit decreased from 4.6 at the first visit to 1.4, and generalized edema was improved, consistent with the body weight lowering from 70 to 62 kg. Moreover, the serum albumin continued rising from 1.4 gm/dL to 2.2 gm/dL. Consequently, in long-term follow-up, the overall clinical of NS remained in remission.

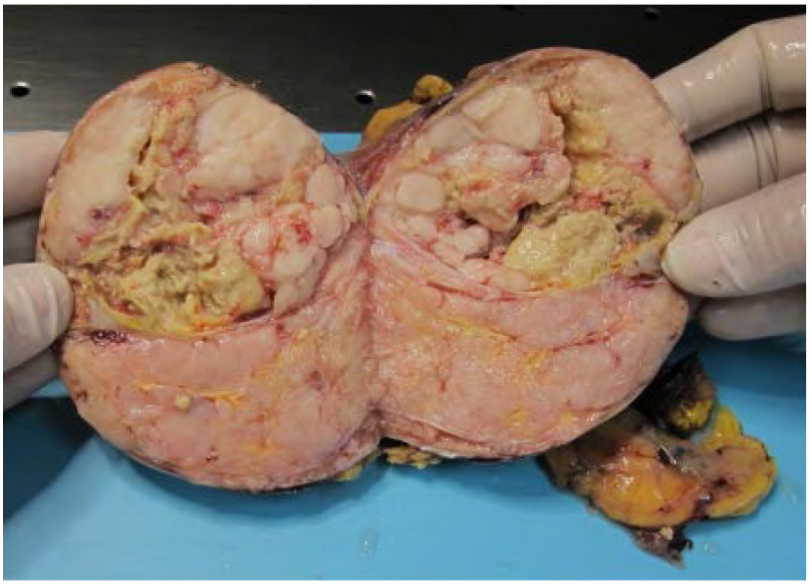

Figure 4. Gross examination of the thymoma showed a well-circumscribed mass surrounded by a partial fibrous capsule and focal irregular borders. Cut surfaces showed a grey, tan mass with lobulated and variegated appearance and revealed hemorrhage and necrosis.

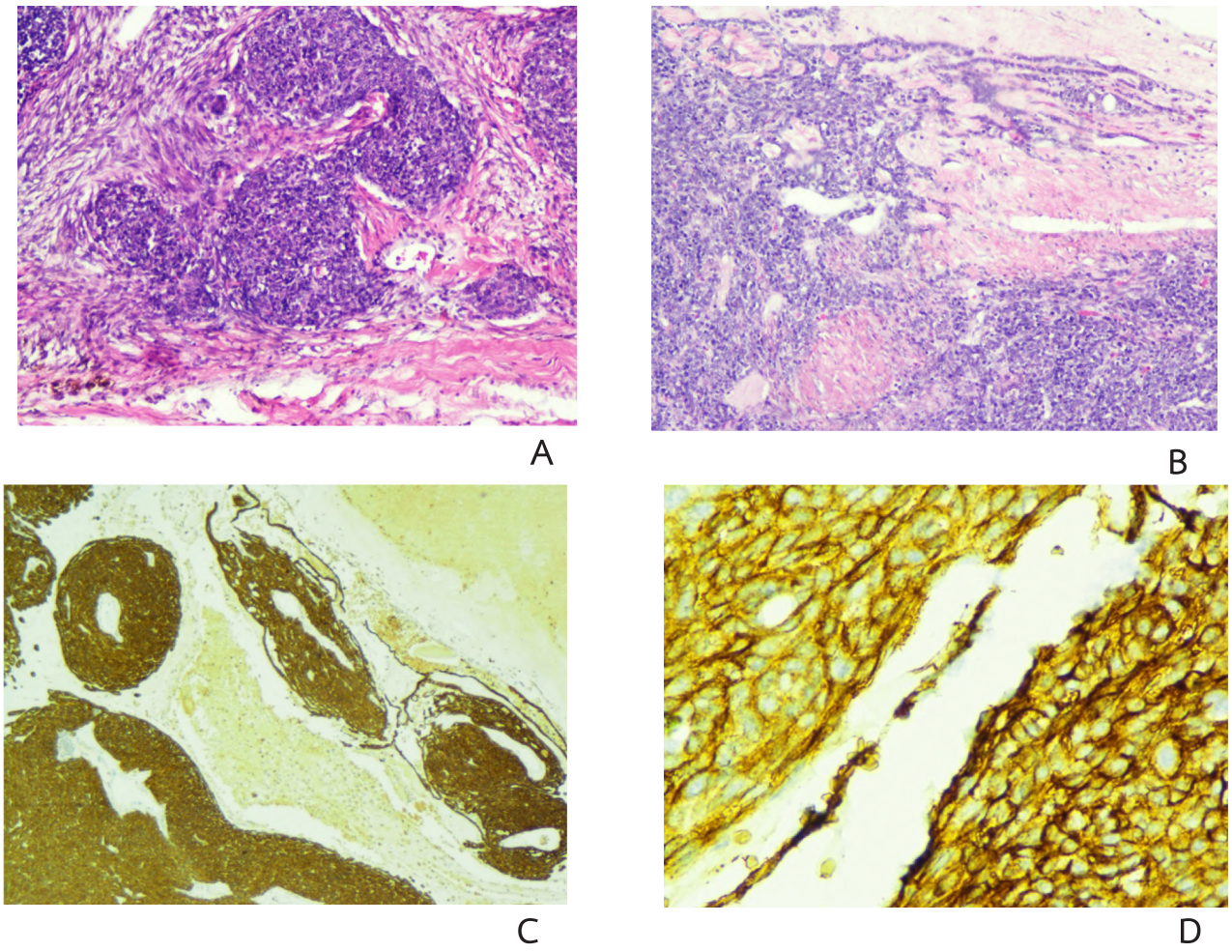

Figure 5. Thymectomy pathology results showed a thymic epithelial tumor, consistent with thymoma type B (A, B), and GLUT1 was strongly positive in thymic carcinoma (C, D).

Thymoma is associated with varied paraneoplastic syndromes such as MG and pure red cell aplasia [1] including case reports of PNS from thymoma. The first reported association of cancer and NS by Lee JC in 1966[11] showed the incidence of PNS during ten years of study was 10%, and nine of eleven histopathologic kidneys were membranous glomerulonephritis. Although the relationship between malignancy to NS remains unclear, the study was the first to describe this relationship due to the immunologic response. Thymoma and NS caused by T-cell mediated are associated with the paraneoplastic explanation.[3-7] Thus, cross-reaction has been observed between eluates from glomeruli and tumor antigens, providing evidence for the role of the immune complex in paraneoplastic glomerulopathy. [12]

Nevertheless, in this case, the patient uncovered a thymoma, and then she developed NS. The kidney biopsy showed FSGS. In this case, clinical findings were like the ordinary NS; the histopathologic result was unusual as PNS. After the thymectomy, overall clinical symptoms improved, suggesting a causative relationship between the two conditions. Accordingly, dysfunction of the immune system, particularly T lymphocytes caused PNS and damaged the podocytes by inflammation due to substances produced by the tumor cells such as cytokines or growth factors that could damage the kidney tissue and disrupt the normal functioning of the glomeruli. This damage led to the formation of scar tissue or sclerosis. FSGS could be a more aggressive disease, with a higher risk of progression to end-stage kidney disease and the need for renal replacement therapy. This case report confirmed that FSGS was one of the PNS.

Finally, the pathophysiology of FSGS is complex and multifactorial. Therefore, further research is needed to understand this disease's mechanisms and develop effective treatments. Moreover, PNS is a rare disorder requiring a multidisciplinary approach involving oncologists and nephrologists to manage underlying cancer and any associated kidney damage.

This case report demonstrates that FSGS is one of the PNS of thymoma. The clinical of NS spontaneously resolved after thymectomy, proposing a causative relationship between the two conditions. Her UPCR decreased from 4.6 to 1.4, and the serum albumin continued rising from 1.4 to 2.2 g/dL. Therefore, when we encounter patients with PNS, maintaining awareness of FSGS is important. Thus, early recognition, work-up and treatment of underlying cancer can preserve the patient's kidneys.

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EFFICACY OF LACTOSE-FREE FORMULA AS A 24-HOUR MANAGEMENT APPROACH FOR ACUTE DIARRHEA AMONG CHILDREN

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Abstract

Background: Diarrhea continues to be a prominent contributor to morbidity and mortality among young children under five years, especially in developing nations. Secondary lactose intolerance is a significant complication that can arise from acute diarrhea. However, it can be effectively managed with lactose-free formula.

Objective: This study aimed to compare the rate of diarrhea resolution within a 24-hour period among children receiving lactose-free formula and those receiving lactose-containing formula.

Methods: This retrospective cohort study took place at Naresuan University Hospital and included 153 children aged between one month and five years admitted with acute diarrhea. Participants with bloody mucous diarrhea suspected to be bacterial in nature, positive stool culture, breastfeeding and chronic diarrhea (including cow's milk protein allergy and inflammatory bowel disease) were excluded. We compared the effectiveness of lactose-free formula (n=48) and lactose-containing formula in improving clinical diarrhea within a 24-hour (n=105).

Results: The study findings indicated the lactose-free formula group demonstrated a statistically significant increase in efficacy, with a 3.90 fold improvement in diarrhea within 24 hours compared with that of the group receiving lactose-containing formula. These results were obtained after the confounding factors were adjusted using multivariable regression analysis. The adjusted relative risk (RR) for a 24-hour improvement in diarrhea was 3.90 (95% CI: 1.91-7.95). However, this study encountered limitations regarding the sample size and accurate measurement of stool output.

Conclusion: Lactose-free formula showed the potential for greater effectiveness in improving acute diarrhea within a 24-hour timeframe compared with lactose-containing formula.

Keywords: Acute diarrhea, Lactose intolerance, Lactose-free formula

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Introduction

Diarrhea remains a significant cause of morbidity and mortality among children, particularly those under five years, especially in developing countries.[1, 2] The etiology of diarrhea can be attributed to bacterial and viral pathogens. In 2019, the Department of Disease Control in Thailand reported that the leading viral causes of diarrhea were rotaviruses (48.8%), followed by norovirus GII (21.3%). The most affected age group was children aged 0 to 4 years, accounting for 74.7% of cases. [3]

Secondary lactose intolerance is a notable complication of acute diarrhea, particularly in cases of viral origin. Younger children with acute viral diarrhea may experience mucosal damage that hinders lactose absorption, leading to lactose intolerance.[4] This intolerance can further exacerbate symptoms of diarrhea and prolong recovery. [5]

The standard approach for lactose intolerance involves using lactose-free formula and restricting foods containing lactose.[6] The ESPGHAN Guidelines for the Management of Acute Gastroenteritis in Children in Europe (2014 update) recommend lactose-free formula among hospitalized children under five years with acute diarrhea but do not routine recommend in outpatient settings.[7] Related studies have investigated the effects of lactose-free formula as an adjunctive treatment for acute diarrhea among children. Ngoenmak conducted a study demonstrating that lactose-free formula reduced the time to reach normal stool consistency to an average of 1.60±0.96 days.[8] Simakachorn et al. reported a median reduction in the duration of diarrhea by 20.5 hours by incorporating lactose-free formula.[9] Furthermore, Hartawan et al. specifically studied children with acute rotaviral diarrhea and observed a mean reduction in duration by 28.38 hours compared with that of the lactose-containing formula.[10] These findings suggest that lactose-free formula may offer a promising approach to shortening the duration of diarrhea and promote faster recovery.

In addition to individual studies, a systematic review conducted by Cochrane in 2013 evaluated lactose-free formula's overall efficacy in reducing diarrhea duration. The review concluded that lactose-free formula resulted in an average reduction of 18.6 hours in the duration of diarrhea.[11] However, a need exists to investigate the effectiveness of lactose-free formula in improving acute viral diarrhea within a 24-hour treatment period, specifically in our community and considering the present time. This study aimed to evaluate the efficacy of lactose-free formula in improving acute viral diarrhea within a 24-hour treatment period.

Methods

This study was approved by the ethics committee of Naresuan University Hospital (COA No. 034/2023. IRB No. P3-0006/2566). A retrospective cohort study collected data from medical hospital records between January 2017 and December 2022. The study population comprised children between the ages of one month and five years who were admitted to the Pediatric Ward at Naresuan University Hospital, Thailand, due to acute viral diarrhea lasting less than seven days, based on clinical manifestations such as fever and URI symptoms. Laboratory investigations revealed no bacterial growth in stool culture and no leukocytosis from CBC. We identified acute diarrhea based on loose stool diarrhea >3 times/day or at least one/day watery stool diarrhea within seven days. Exclusion criteria included bloody mucous stool, suspected bacterial diarrhea, positive stool culture, cow's milk protein allergy, breastfeeding and chronic diarrhea. Data were collected from medical hospital records including age, sex, underlying diseases, time to recover from diarrhea and adjunctive treatment received. The primary objective was to compare the effectiveness of lactose-free formula versus lactose-containing formula in managing acute viral diarrhea. Clinical improvement in 24 hours was defined as the presence of normal stool consistency or decreased frequency of diarrhea.

Statistical Analysis

Baseline characteristics were presented as frequencies and percentages reported using Fisher's exact test. Univariate and multivariable regression analyses were performed to compare

the efficacy between the two groups, reporting crude relative risks (RR) and adjusted RR. Statistical analysis was conducted using the Stata Program.

Results

Of the initial 191 patients considered for inclusion, 38 were excluded based on the predetermined exclusion criteria. The final analysis included 153 patients, with 48 receiving lactose-free formula and 105 receiving lactose-containing formula **(Figure 1)**. The study population consisted of 56.21% male and 43.79% female patients, with 35.95% of patients being below 1 year old (**Table 1**). Most patients had no underlying diseases. Both groups (lactose-free formula and lactose-containing formula) exhibited a mean diarrhea at 1.60±0.10 days before admission. Most presented moderate dehydration (86.72%) and the initial laboratory results showed no metabolic acidosis, either the lactose-free formula or lactose-containing group (**Table 1**). All patients in this study received initial intravenous infusion for rehydration upon admission. Totally, 46 patients did not receive any of the administered adjunctive treatments including zinc solution,

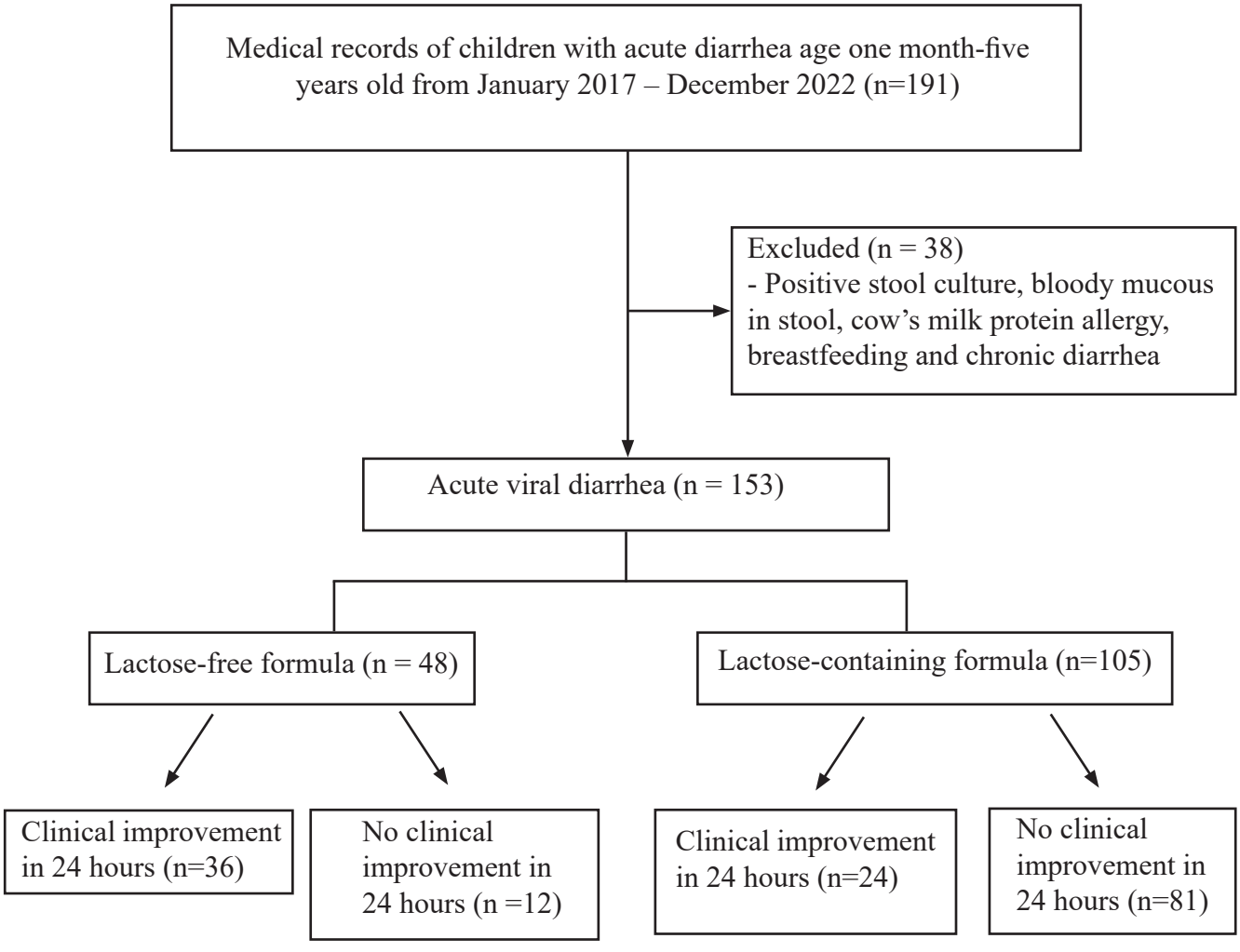

Figure 1. Study flow diagram

Table 1. Demographics and characteristics of children with acute viral diarrhea

Characteristics	Lactose-free formula (n = 48)	Lactose-containing formula (n = 105)	*p*-value
Age (%)			0.366
< 1 year old	20 (41.67)	35 (33.33)	
1 -5 years old	28 (58.33)	70 (66.67)	
Sex (%)			0.861
Male	28 (58.33)	58 (55.24)	
Female	20 (41.67)	47 (44.76)	
Degree of dehydration (%)			0.509
Mild	4 (8.33)	15 (14.29)	
Moderate	43 (89.58)	89 (84.76)	
Severe	1 (2.08)	1 (0.95)	
Stool pH < 5.5 (%)	34 (73.91)	21 (33.33)	< 0.001
Metabolic acidosis (%)			0.656
Yes (serum bicarbonate ≤ 15 mmol/L)	10 (21.74)	18 (18.37)	
No (serum bicarbonate > 15 mmol/L)	36 (78.26)	80 (81.63)	
Adjustive Therapy			
None	15 (31.25)	31 (29.52)	0.851
Racecadotril	4 (8.33)	3 (2.86)	0.679
Zinc solution	11 (22.92)	21 (20.00)	0.674
Zinc + Racecadotril	15 (31.25)	40 (38.10)	0.470
Probiotic+Racecadotril	0 (0)	2 (1.90)	0.470
Zinc solution, Racecadotril, and Probiotics	3 (6.25)	8 (7.62)	0.528

racecadotril and probiotics. Seven patients received racecadotril alone, 32 patients were administered zinc solution, 55 patients received zinc solution and racecadotril combined, 2 patients received racecadotril and probiotics and 11 patients received racecadotril along with zinc solution and probiotics. When comparing the two groups (lactose-free and lactose-containing formula), no significant difference was observed, except in the lactose-free formula group, 34 patients (73.91%) presented a stool pH value of <5.5. This finding significantly differed from the lactose-containing group, where only 21 patients (33.33%) had a stool pH of <5.5 (**Table 1**).

Table 2. The primary outcome of the study

Outcome	Crude RR (95%CI)	Adjusted RR (95%CI)
Diarrhea improvement in 24 hours after treatment	3.28 (2.23- 4.83)	3.90 (1.91-7.95) *

* Adjusted age, gender, dehydration, stool pH, metabolic acidosis, and adjunctive therapy.

The efficacy of lactose-free formula in treating acute diarrhea was determined by measuring the improved clinical diarrhea within 24 hours. Multivariable regression analysis revealed that the lactose-free formula group had a 3.90 fold higher rate of improvement than that of the lactose-containing formula group. Crude relative risk (RR) was calculated as 3.28 (2.23-4.83). Furthermore, after adjusting the age, sex, dehydration, stool pH, metabolic acidosis and adjunctive therapy, the adjusted RR was 3.90 (1.91 to 7.95) (**Table 2**). Using subgroup analysis within the lactose-free formula group (n=48), a comparison was made between the zinc solution-only with the other three groups: (1) no adjunctive treatment, (2) racecadotril group and (3) zinc solution combined with racecadotril. The analysis revealed that the improved rate in these groups was lower by 15% ($p = 0.851$), 8.33% ($p = 0.679$) and 15% ($p = 0.470$), respectively.

Discussion

Lactose intolerance frequently arises as a complication of acute viral diarrhea, particularly among children under 5 years. In our study involving 153 children, 75% of participants receiving lactose-free formula demonstrated improvement within 24 hours. We specifically selected this time frame to assess the efficacy of treatment in cases of acute diarrhea. Related studies demonstrated the ability of the lactose-free formula to reduce the duration of diarrhea.[7-10] Specifically, among children aged 1 month to 5 years admitted with acute viral diarrhea, the rate of improved clinical diarrhea within 24 hours was 3.90 times higher in the lactose-free formula group compared with that in the lactose-containing group. These results aligned with the recommendations outlined in the clinical practice guidelines for acute diarrhea among children. The Thai Society of Pediatric Gastroenterology and Hepatology, 2019 guidelines recommend[2] using lactose-free formula as a viable option for children under 5 years requiring hospital admission and those exhibiting evidence of lactose intolerance. Similarly, the ESPGHAN guidelines to manage acute gastroenteritis among children in Europe[7] advocate using lactose-free formula among hospitalized children under 5 years with acute diarrhea. Most children enrolled in our study required hospital admission due to moderate dehydration, further emphasizing the practical relevance of our findings in real-world clinical settings. In our study, stool pH emerged as a statistically significant factor, with a higher proportion of patients in the lactose-free formula group exhibiting a stool pH <5.5. Stool pH has been used as a screening tool for carbohydrate malabsorption in related studies.[12] Despite its limitations in terms of sensitivity and specificity [13] this diagnostic tool can provide valuable information in certain clinical contexts. Regarding adjunctive therapy for acute diarrhea, our study did not identify any statistically significant differences between the groups administered with lactose-free and lactose-containing formulas. However, subgroup analysis performed on patients receiving lactose-free formula revealed a better trend regarding improvement within 24 hours when treatment consisted solely of zinc solution, as compared with other groups with different treatment interventions (no adjunctive treatment, racecadotril only and combined therapy of zinc solution and racecadotril). Interestingly, our findings showed that the group receiving zinc solution alone had a shorter mean length of stay (2.91 ± 0.10 days) compared with the other groups (no adjunctive treatment, racecadotril and zinc solution combined with racecadotril), which indicated a mean length of stay of three days. Although the participants in this study demonstrated clinical improvement in diarrhea within 24 hours, a hospital observation period of 2 to 3 days remained necessary before their discharge. However, acknowledging the limitations of our study is important, including incomplete data regarding the length of the hospital stay and a small sample size. Additionally, the accuracy of stool output measurement was not ensured, and certain data were unavailable. Further research using larger sample sizes and comprehensive data collection is warranted to validate and expand upon our findings.

Conclusion

Our study provides evidence supporting the superior efficacy of lactose-free formula compared with lactose-containing formula in the dietary management of acute viral diarrhea among children aged 1 month to 5 years old, within a 24-hour timeframe. The concurrent administration of zinc solution and lactose-free formula may lead to a higher rate of improvement and shorter hospital stays. These findings suggest that including lactose-free formula as a complementary measure in the dietary management plan has the potential to reduce costs and shorten the duration of hospitalization for children receiving a diagnosis of acute diarrhea.

Conflicts of Interest

The authors declare they have no conflict of interest regarding the publication of this article.

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CANCER RATIO-BASED DIAGNOSTIC TOOL IN IDENTIFYING MALIGNANT PLEURAL EFFUSION: SENSITIVITY, SPECIFICITY AND CLINICAL INSIGHTS

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Abstract

Background: Malignant pleural effusion (MPE) is a common cause of exudative lymphocytic pleural effusion. Although pleural fluid evaluation is routinely performed, cytology or histopathology remains the gold standard for MPE diagnosis. The cancer ratio (CR), calculated by comparing serum LDH to pleural fluid ADA levels, has shown promise in diagnosing MPE. However, no studies have investigated its utility in the Thai population, which has a high tuberculosis prevalence.

Objectives: This study aimed to evaluate the diagnostic accuracy of the CR in MPE diagnosis, compare clinical and pleural fluid parameters between MPE and nonMPE cases, determine the appropriate CR cut-off for the Thai population and develop a prediction score for prediagnosing MPE.

Results: Between July 2021 and December 2022, patients presenting exudative lymphocytic pleural effusion were included in the study. Demographics, symptoms, radiographic findings and pleural fluid parameters were collected and cytology/histopathology served as the reference test. CR performance was assessed using receiver operating characteristic curves, and a prediction score was developed using multivariable logistic regression analysis. Among 122 patients, 46.7% received a diagnosis of MPE. The CR exhibited a sensitivity of 87.7% and specificity of 72.3% (AUC 0.83) with a cut-off level >10. Patients with MPE showed longer symptom duration, lower fever and massive pleural effusion, which were more common in MPE than nonMPE cases. A prediction score incorporating symptom duration, fever history, effusion amount and CR demonstrated superior diagnostic performance for MPE (AUC 0.94) compared with the CR alone.

Conclusion: The CR can effectively differentiate MPE from nonMPE among patients with exudative lymphocytic pleural effusion. A cut-off level >10 is recommended for diagnosing MPE in the Thai population. Combining clinical, radiologic and CR data may aid in prediagnosing MPE; however, further research is needed for validation.

Keywords: cancer ratio, malignant pleural effusion, exudative, lymphocytic, pleural effusion

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Introduction

Exudative lymphocytic pleural effusion. is primarily attributed to two leading causes: malignant pleural effusion (MPE) and tuberculous pleural effusion (TPE).[1, 2] These conditions account for 58% of exudative pleural effusion cases in Thailand.[3] Thoracentesis is commonly performed to assess pleural fluid parameters as an initial step in the differential diagnosis of these diseases. A crucial parameter for diagnosing TPE is pleural fluid ADA (pADA), which exhibits a sensitivity of 92% and specificity of 90% when using a cut-off value above 40 IU/L.[4, 5] However, for MPE, the gold standard remains cytology or histopathology with pleural fluid cytology yielding an average diagnostic rate of 60%.[2, 6] Image-guided pleural biopsy increases the diagnostic yield to 87%, while thoracoscopy achieves a rate of 94.8%.[6-8] These latter methods involve more invasive procedures. Related studies have investigated using biochemical markers such as tumor markers (CEA, CA-125, CA 19-9, CA 15-3 and CYFRA 21-1) in pleural fluid. While these markers display a relatively high specificity of approximately 80 to 90%, their sensitivity remains low, ranging from 40 to 60%.[9, 10] Moreover, their routine use in clinical practice remains unfeasible, and additional costs are associated with these tests.

One related study[11] demonstrated the significant predictive value of the cancer ratio (CR) in diagnosing MPE (MPE). The CR is calculated as the serum LDH (sLDH) ratio to pleural fluid ADA (pADA). Using a cut-off value greater than 20, the CR showed a sensitivity of 0.98 (95% CI 0.92-0.99) and a specificity of 0.94 (95% CI 0.83-0.98). Both sLDH and pADA are commonly used to evaluate patients with exudative lymphocytic pleural effusion to distinguish between different diseases.[6, 12] However, noting that the CR has not been investigated in the Thai population is important because it indicates a high prevalence of tuberculosis. As a result, the accuracy of this parameter and the choice of an appropriate cut-off level may be influenced, which forms the basis of the current study. The study aimed to investigate the diagnostic accuracy of the CR for MPE among patients presenting a lymphocytic-predominant profile.

Methods

Participants

From July 2021 to December 2022, a prospective enrollment of patients with recently diagnosed pleural effusion was conducted at Phramongkutklao Hospital. The eligibility criteria encompassed individuals aged ≥20 years, exhibiting an exudative profile ascertained through rigorous adherence to Light's criteria and lymphocytes constituting more than 50% of nucleated cells. Notably, patients receiving a diagnosis of pseudo-exudative pleural effusion, expectant mothers, those who declined to undergo invasive procedures and individuals in an advanced stage of disease or receiving palliative care were excluded from participation. Additionally, conditions that could cause an elevation in serum lactate dehydrogenase (LDH) such as liver disease, severe anemia (hemoglobin <8 g/dL), heart attack within two weeks, bone fractures, muscle trauma, recent organ infections and HIV, were also excluded. This study was approved by the ethics committee of the Royal Thai Army Medical Department (approval No. R003h/65).

Data collection

The demographic data, comorbidities, personal history of cancer, history of tuberculosis exposure, symptoms, initial radiological findings and pleural fluid parameters were collected following patients' diagnosis of exudativelymphocytic pleural effusion. As part of the study protocol, all participants had cytology or histopathology testing, serving as the standard reference test for differentiating between MPE and nonMPE. The pathologists confirmed that the diagnosed MPE revealed the presence of malignant cells in cytology or histopathology.

Outcomes

The primary objective of this study was to determine the diagnostic performance of the CR in diagnosing MPE, explicitly assessing its sensitivity and specificity. The secondary

endpoints included determining the prevalence of MPE, comparing clinical characteristics and pleural fluid parameters between MPE and nonMPE cases and developing a predictive score for diagnosing MPE.

Statistical analysis

Based on the prevalence of MPE reported in a related systematic review on the CR, which was 40.8%[13], the sample size was calculated to be 118 subjects, with a minimum of 48 subjects diagnosed with MPE. Descriptive statistics, such as frequencies, means (SD), or medians (interquartile range [IQR]), were used depending on the distribution of the data. Categorical variables were compared using the chi-square test, while continuous variables were also compared using the Mann-Whitney U test between the MPE and non MPE groups. A two-sided p <0.05 was considered statistically significant. The primary outcome was assessed using the receiver operating characteristic (ROC) curve analysis, and multivariate analyses were conducted using a logistic regression model for the secondary endpoints. The data, including pleural fluid cell analysis, pleural fluid protein, pleural fluid LDH, pleural fluid ADA and serum LDH, underwent categorization into ranges. This categorization was determined by referring to a related study for established reference points.[4, 10, 14, 15] All data were analyzed using statistical software (STATA, Version 14).

Model development

Our model development involved complete-case analysis, meaning we did not perform data imputation. We included all relevant clinical parameters in a multivariable logistic regression model to identify significant predictors of MPE. To decide which predictors to keep, we used backward elimination based on two criteria: statistical significance indicated by the *p*-value of each predictor and the overall predictive performance of the model measured by the area under the ROC (AuROC) curve. Initially, we eliminated noncontributing factors with large *p*-values and the lowest effect size (odds ratio closest to 1.00) from the regression model. After removing each predictor, we assessed the model's diagnostic performance using the AuROC. If removing a predictor led to a significant decrease in AuROC, we reintroduced that predictor back into the model. We repeated these steps consecutively until all remaining predictors in the model had a *p*-value lower than 0.10, ensuring that the reduced model maintained a satisfactory AuROC. To evaluate the discrimination and calibration of the final reduced model, we used AuROC curves and conducted the Hosmer-Lemeshow goodness-of-fit test.

Score derivation and validation

Scores were assigned to each predictor in the final model based on their logit coefficients. During score transformation, the denominator was set as the lowest coefficient among all predictors, and the other coefficients were used as numerators. After dividing the coefficients, the products were rounded to whole numbers. Subsequently, scores were calculated for each patient in the development cohort. We conducted discrimination and calibration measures in the logistic regression model based on the scores. The scores were further divided into three risk groups: low, moderate and high probability of having MPE, using an appropriate cut-off point.

Results

A total of 302 patients were diagnosed with pleural effusion, and after applying the predefined inclusion criteria, 154 patients were considered eligible for the study. Subsequently, 12 cases of undiagnosed pleural effusions, 15 cases with incomplete data, one patient with both TPE and MPE and four patients with palliative or end-stage diseases were excluded. As a result, a final dataset of 122 patients was available for analysis, as depicted in **Figure 1.** Among these patients, 57 individuals (46.7%) received a diagnosis of MPE, while the origins of the MPEs and the etiologies of nonMPE cases are presented in **Table 2.**

Table 1 shows the baseline clinical-radiologic and analytic characteristics of the patients. Most participants were male, comprising

approximately 54% of the total sample. The mean age of the participants was 61 years with the MPE group being significantly older (p=0.01). No significant differences were observed between the two groups regarding smoking history and history of tuberculosis exposure. However, patients with MPE exhibited a higher prevalence of personal cancer history, accounting for 41.8% of cases, significantly greater than that observed in the nonMPE group.

Patients with MPE displayed notable clinical symptoms persisting for more than 30 days (p = 0.01) and a lower incidence of fever than patients with nonMPE. However, the two groups showed no significant difference regarding other symptoms such as dyspnea, chest pain, cough or weight loss. Additionally, a higher proportion of patients with MPE exhibited massive pleural effusion, characterized by the involvement of over two thirds of the hemithorax during the initial evaluation, in contrast to patients with nonMPE (33.3% vs. 10.8%, p=0.002). Furthermore, patients with MPE demonstrated a significantly higher median CR than non-patients with nonMPE (20.7 vs. 5.1, $p < 0.001$).

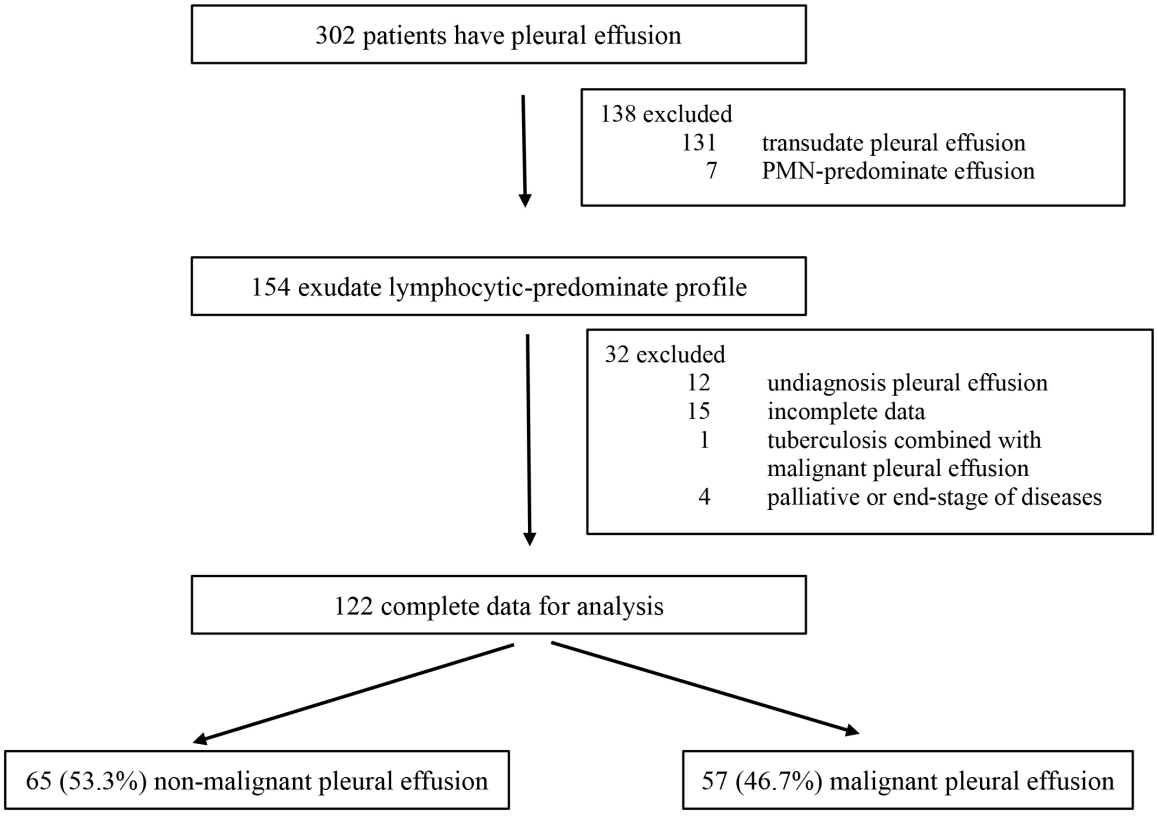

Figure 1. Study flow of patient enrollment

Table 1. Baseline demographic data, presenting symptoms, radiographic data and initial laboratory investigation of derivation cohort, comparison of MPE and nonMPE

Characteristics	non-MPE (N=65)	MPE (N=57)	*p*-value
Age (year), mean ± SD	57.2±18.4	66.2±13.6	0.01*
Male, N (%)	37 (56.9)	29 (50.9)	0.50
Current or ex-smoker, N (%)	20 (35.1)	12 (24.5)	0.24
Contact TB, N (%)	8 (13.8)	4 (7.7)	0.31
Underlying cancer, N (%)	12 (18.8)	23 (41.8)	0.01*
- Lung cancer	1 (1.5)	7 (12.3)	
- Breast cancer	2 (3.1)	7 (12.3%)	
- Hematologic malignancy	3 (4.6)	2 (3.5)	
- Other cancer type	6 (9.2)	7 (12.3)	
CKD over stage 3, N (%)	14 (21.5)	4 (7.4)	0.03*
Duration of symptom (day), median (IQR)	30 (10-60)	30 (30-90)	0.01*
Symptoms, N (%)			
Dyspnea	48 (76.2)	51 (89.5)	0.06
Chest pain	19 (30.6)	17 (31.5)	0.92
Fever	39 (62.9)	2 (3.8)	< 0.001*
Cough	37 (59.7)	33 (62.3)	0.78
- Anorexia	17 (29.3)	15 (31.3)	0.83
- Weight loss	32 (55.2)	25 (52.1)	0.75
Pleural fluid appearance, N (%)			0.14
- Serous	49 (75.4)	34 (61.8)	
- Serosanguinous	15 (23.1)	21 (38.2)	
- Purulent	1 (1.5)	0	
Pleural fluid location, N (%)			0.16
- Right	39 (60)	25 (43.9)	
- Left	19 (29.2)	26 (45.6)	
- Bilateral	7 (10.8)	19 (33.3)	
Massive PF, N (%)	7 (10.8)	19 (33.3)	0.002*
PF WBC, median (IQR)	1443 (555-2560)	1512 (677-2213)	0.05
PF Lymphocytes (%), mean±SD	87.2±11.6	82.9±13.4	0.37

Table 1. Baseline demographic data, presenting symptoms, radiographic data and initial laboratory investigation of derivation cohort, comparison of MPE and nonMPE (Cont.)

Characteristics	non-MPE (N=65)	MPE (N=57)	*p*-value
PF protein (g/dL), mean±SD	5.0±1.1	4.8±1.1	0.08
PF LDH (U/L), median (IQR)	275 (179-514)	364 (232-633)	0.40
PF ADA (U/L), median (IQR)	45 (24.7-58.9)	13.6 (10.3-18.5)	< 0.001*
Serum LDH (U/L), median (IQR)	228 (190-270)	279 (221-352)	0.001*
Cancer ratio, median (IQR)	5.1 (3.6-11.5)	20.7 (16-30)	< 0.001*

* *p*-value < 0.05

MPE malignant pleural effusion, *TB* Tuberculosis, *CKD* chronic kidney disease, *PF* pleural fluid, *LDH* lactate dehydrogenase, *ADA* adenosine deaminase

Table 2. Origin of MPE and etiologies of nonMPE

Origin (n=57)		Etiology (n=65)	
Lung	27 (47.4%)	Tuberculous pleural effusion	49 (75%)
Breast	8 (14.0%)	Others	16 (25%)
Hematologic	3 (5.3%)	- Meigs syndrome or Pseudo-meigs syndrome	
Mesothelioma	1 (1.8%)		
Poorly differentiated carcinoma unclassified	7 (12.3%)	- Radiation pleuritis - Uremic pleuritis	
Others	11 (19.3%)	- Pulmonary embolism - Post-CABG - Pleural cysticercosis	

CABG coronary artery bypass grafting

As depicted in **Figure 2** and **Table 3**, the primary outcome demonstrates that the CR is highly accurate in predicting MPE when a cut-off level >10 is used with a sensitivity of 87.7% and specificity of 72.3% (AUC 0.83). Regarding the secondary endpoint, no statistically significant differences between the MPE and nonMPE groups were found regarding pleural fluid appearance and location. Similarly, no significant variations were observed in total white blood cell (WBC) count, lymphocyte count (%), protein level and LDH level in the pleural fluid profile between the two groups. However, the pleural fluid adenosine deaminase (pADA) level was significantly lower in the MPE group (median 13.6 vs. 45.0, p <0.001). **Table 4** shows multivariate analysis revealed that only a CR value higher than 10 remained significantly elevated in the MPE group with an adjusted odds ratio of 15.26 (p=0.01). Conversely, a pADA value less than 40 IU/L and sLDH higher than the upper normal limit did not show significant differences.

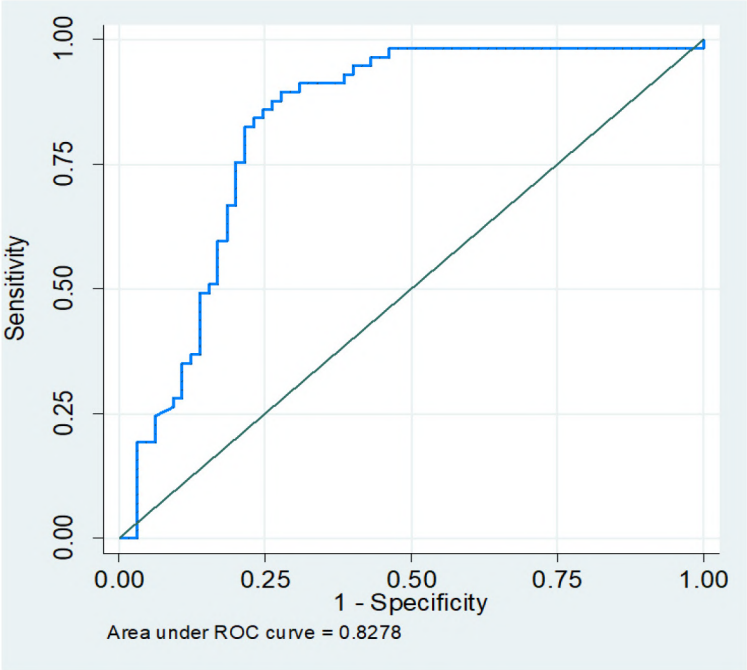

Figure 2. ROC curve of cancer ratio for diagnosis of malignant pleural effusion

Table 3. Cancer ratio sensitivity and specificity at different cut-off levels

Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	ROC area	LR (+) (95% CI)	LR (-) (95% CI)	PPV (95% CI)	NPV (95% CI)
>10	87.7 (76.3-94.9)	72.3 (59.8-82.7)	0.80 (0.73-0.87)	3.17 (2.11-4.75)	0.17 (0.08-0.35)	73.5 (61.4-83.5)	87 (75.1-94.6)
>20	56.1 (42.4-69.3)	83.1 (71.7-91.2)	0.70 (0.62-0.78)	3.32 (1.85-5.96)	0.53 (0.39-0.72)	74.4 (58.8-86.5)	68.4 (56.9-78.4)
>30	24.6 (14.1-37.8)	93.8 (85-98.3)	0.59 (0.53-0.66)	3.99 (1.39-11.44)	0.8 (0.68-0.94)	77.8 (52.4-93.6)	58.7 (48.6-68.2)
>40	10.5 (4-21.5)	96.9 (89.3-99.6)	0.54 (0.49-0.58)	3.42 (0.72-16.28)	0.92 (0.84-1.02)	75 (34.9-96.8)	55.3 (45.7-64.6)
>50	7 (1.9-17)	96.9 (89.3-99.6)	0.52 (0.48-0.56)	2.28 (0.43-11.99)	0.96 (0.88-1.04)	66.7 (22.3-95.7)	54.3 (44.8-63.6)
>60	3.5 (0.4-12.1)	96.9 (89.3-99.6)	0.5 (0.47-0.53)	1.14 (0.17-7.84)	1 (0.93-1.06)	50 (6.8-93.2)	53.4 (44-62.6)

PPV positive predictive value, *NPV* negative predictive value, *PLR* positive likelihood ratio, *NLR* negative likelihood ratio, *CI* confidence interval

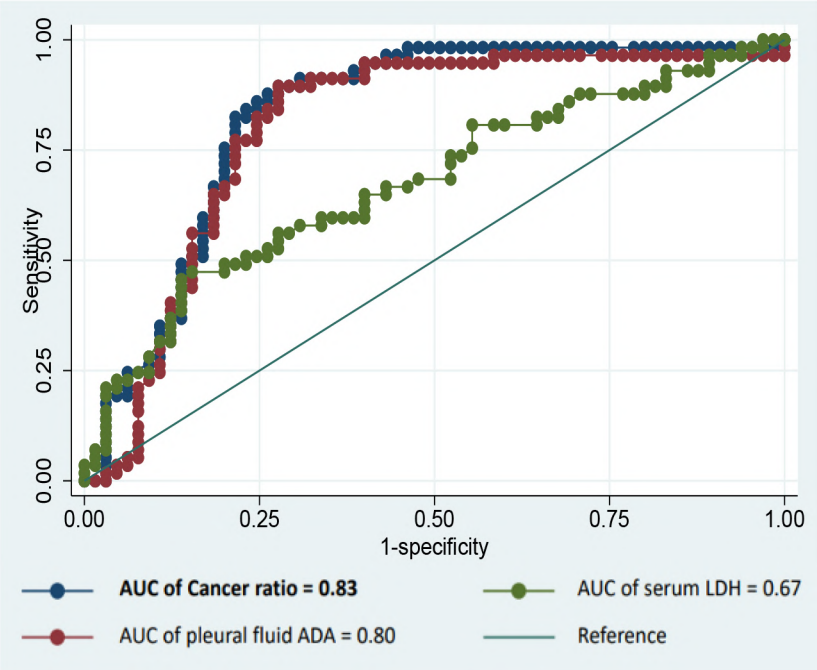

Table 4. Univariable and multivariable analysis of PF profiles with malignant pleural effusion as the outcome variable

Variables	Crude OR (95% CI)	*p*-value	mOR* (95% CI)	*p*-value
PF WBC > 2,000/mm3	1.01 (0.48 – 2.14)	0.97	3.41 (0.41 – 28.57)	0.26
PF %lymphocyte > 80%	0.44 (0.19 – 1.02)	0.06	0.19 (0.02 – 1.80)	0.15
PF protein < 4.0 g/dL	1.32 (0.51 – 3.39)	0.56	4.63 (0.44 – 49.04)	0.20
PF LDH > 1,790 U/L	1.15 (0.07 – 18.75)	0.92	7.17 (0.03 – 2028.93)	0.49
PF ADA < 40 IU/L	25.33 (7.16 – 89.57)	<0.001	18.51 (0.67 – 513.37)	0.09
Serum LDH > 225 U/L	2.34 (1.10 – 4.97)	0.03	2.28 (0.35 – 14.99)	0.39
Cancer ratio > 10	18.65 (7.14 – 48.69)	< 0.001	15.26 (1.88 – 124.10)	0.01

*Logistic regression model adjusted with age > 60 years, gender, comorbidities, duration of symptom > 60 days, symptoms, and radiography.

PF pleural effusion, *WBC* white blood cell, *LDH* lactate dehydrogenase, *ADA* adenosine deaminase

When analyzing patients based on their pADA levels, all three patients with pADA levels of 40 U/L or higher (typically diagnosed as TPE had MPE. The etiology of MPE in these cases was hematologic malignancy, and one of the three patients had a CR greater than 10. Among patients with pADA levels less than 40 U/L, 52 out of 80 cases were diagnosed as MPE. Utilizing a CR > 10 resulted in a high sensitivity of 90.7% in diagnosing MPE. Evaluating the predictability of MPE was performed using the CR, serum LDH (sLDH) and pADA; the CR exhibited the highest area under the receiver operating characteristic (ROC) curve for predicting MPE (**Figure 3**). However, the ROC curve of CR was still comparable with pADA (p=0.22).

Developing a predictive score using the multivariable reduced logistic model for the derivation of the scoring system incorporating clinical factors such as the duration of symptoms and history of fever, radiologic factors such as the amount of pleural effusion and the CR with weighted scores (using a cut-off level >10), we obtained a total score of 17.5 (**Table 5**). Our findings indicated that using this predictive score significantly enhanced the accuracy of diagnosing MPE, as demonstrated by an area under the curve (AUC) of 0.94 (**Figure 4).** The p-value via the Hosmer-Lemeshow goodness-of-fit test was 0.78. The calibration plot of the final model is shown in **Figure 5.** After comparing the predictive score with the clinical score and clinical score plus pleural fluid ADA, the CR demonstrated improved diagnostic performance when added to clinical criteria alone (AUC 0.87, p=0.01) but was comparable with clinical criteria plus ADA (AUC 0.93, p=0.69) **(Figure 6).**

Each potential predictor in the multivariable model was assigned a specific score based on its logistic regression coefficient. The scoring scheme resulted in a total score ranging from 0 to 17.5. They were further divided in three risk subcategories to make the scores more clinically applicable. This categorization was determined by examining the calibration plot, showing the relationship between the probability of having MPE and the distribution of scores. The low risk group had scores ranging from 0 to 5, the moderate risk group had scores ranging from 6 to 14.5 and the high risk group had scores ranging from 14.5 to 17.5. For each risk group, the positive predictive values were calculated. The low risk group had a positive predictive value of 0, the moderate risk group had a positive predictive value of 48.21 (95%CI 35-62), and the high risk group had a positive predictive value of 96.15 (95%CI 80-99) **(Table 6)**.

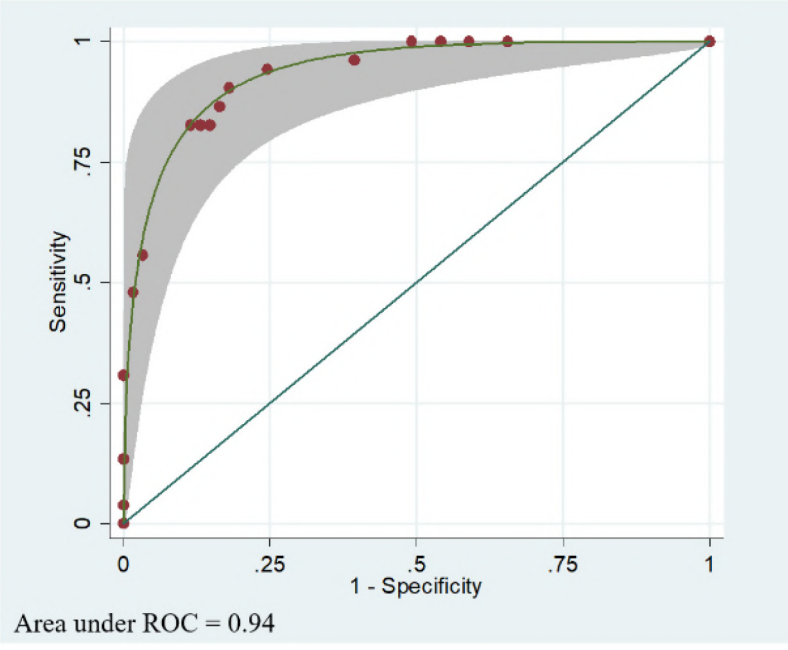

Figure 4. ROC of predicted score to diagnose malignant pleural effusion

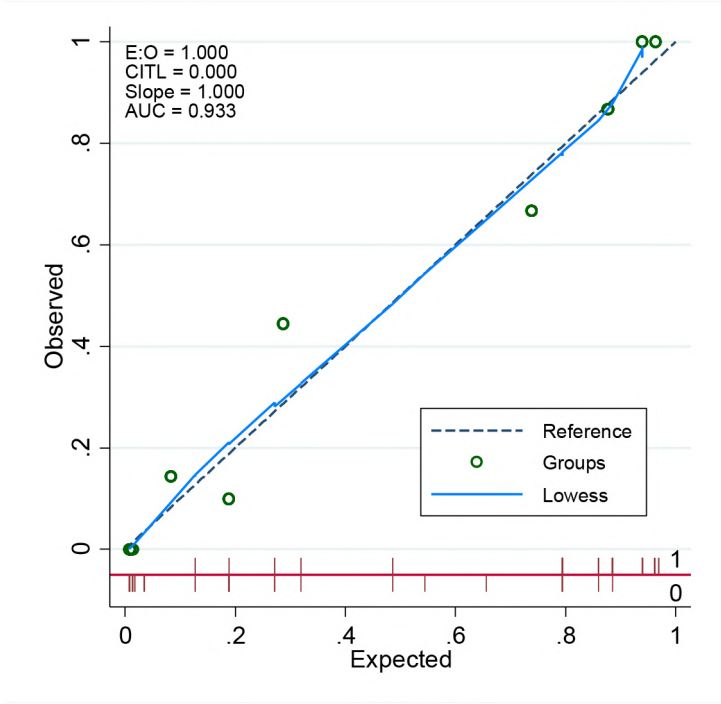

Figure 5. Calibration plot of prediction model performance

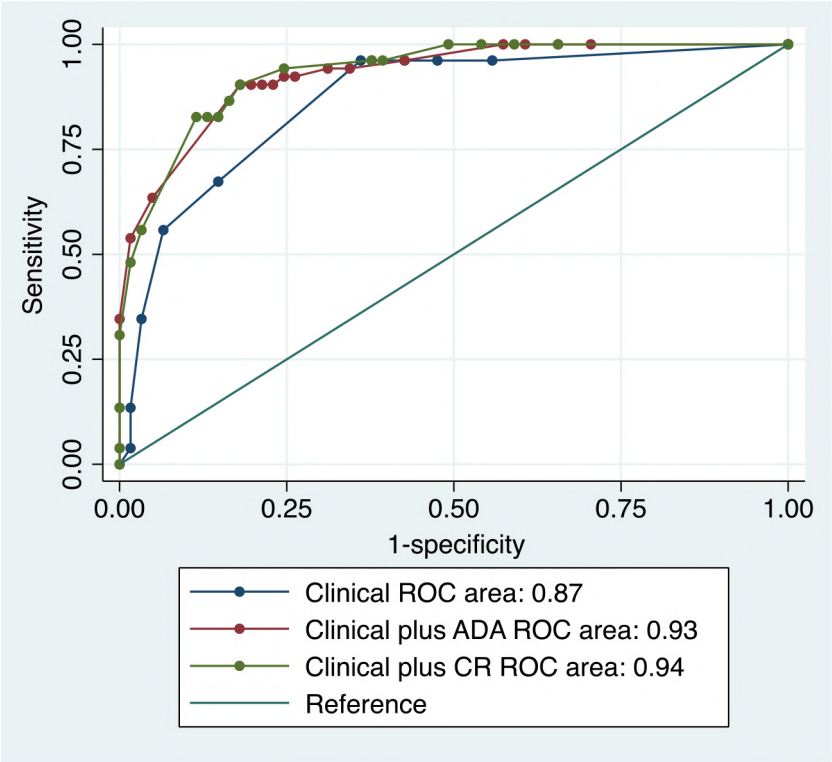

Figure 6. ROC curve compares clinical, clinical with pleural fluid ADA <40 U/L, and predicted model for diagnosis of malignant pleural effusion

Table 5. Risk score deviation using multivariable logistic regression coefficients

Potential predictors	Odds ratio	95% confidence interval	*p*-value	Coefficients	Score
Duration of symptom (days)					
0 – 29 days	1	Reference	-	-	0
30 – 60 days	1.58	0.33 – 7.49	0.56	0.46	1
> 60 days	2.00	0.44 – 8.96	0.37	0.69	1.5
Fever					
Yes	1	Reference	-	-	0
No	29.00	5.31 – 158.57	< 0.001	3.37	7
Chest radiography					
Non-massive PF	1	Reference	-	-	0
Massive PF	4.11	0.89 – 19.02	0.07	1.41	3
Cancer ratio > 10	15.5	4.57 – 52.53	< 0.001	2.74	6
Total score					17.5

Table 6. Distribution of nonMPE vs. MPE across different levels of risk categories (low, moderate, and high risk)

Risk categories	Score	Non-MPE	MPE	PPV	95% confidence interval	*p*-value
Low	0 - 5	31 (100%)	0	0	0 – 11	< 0.001
Moderate	6 – 14.5	29 (51.8%)	27 (48.2%)	48.21	35 – 62	< 0.001
High	> 14.5	1 (3.9%)	25 (96.1%)	96.15	80 – 99	< 0.001

MPE malignant pleural effusion, *PPV* positive predictive value

Discussion

This study constitutes the first to investigate the CR diagnostic accuracy in predicting MPE among Thai patients. The findings demonstrated that the CR displayed good accuracy, as indicated by an AUC value of 0.83, consistent with one related study.[11] Importantly, a CR >10 was identified as the optimal threshold, resulting in a sensitivity of 87.7% and specificity of 72.3%. These results closely resembled those of related studies.[3, 9, 16, 17] The cut-off value for CR was also similar to that in one study conducted in China.[17] However, our values were lower when comparing the sensitivity and specificity of our study to those reported in a related meta-analysis.[13, 18] This difference may be attributed to the specific focus of our study on patients with an exudative lymphocytic profile, while related studies encompassed patients with an exudative profile in general.

In this study, the most common causes of exudative lymphocytic pleural effusion were MPE and TPE, accounting for most cases in the nonMPE group. The prevalence rates for MPE and TPE were 46.7 and 40.2%, respectively. Within the MPE group, a longer duration

of symptoms, a personal history of cancer and an absence of fever were more frequently observed. Furthermore, massive pleural effusion on radiographic findings significantly favored the diagnosis of MPE. These findings are consistent with a related study[3] comparing TPE and MPE. Regarding plNo, a significant difference was observed between MPE and non MPE groups regarding pleural fluid appearance, with a trend toward a higher proportion of serosanguinous fluid in the MPE group (38.2% vs. 23.1%).

This significantly higher CR in the MPE group may be partially attributed to the significantly lower levels of pADA than in the non-MPE group. However, we cannot conclude that a pADA level < 40 indicates the presence of MPE is essential, as currently, a lack of clear studies establishing the accuracy and optimal cut-off level of pADA in MPE diagnosis. Furthermore, the cut-off level of pADA used for diagnosing TPE in the Thai population may be lower than the current standard of 40.[3, 16] The advantage of the CR is that it may assist in diagnosing MPE, especially when pADA levels are low. In routine clinical practice, patients presenting lymphocyte-predominated exudative pleural effusion and diminished pADA levels are frequently excluded from diagnosing TPE. However, those individuals exhibiting elevated CR levels may carry a heightened likelihood of experiencing MPE, warranting a prompt and thorough investigation to establish a definitive diagnosis. Based on ROC curve analysis, the CR still exhibited better diagnostic accuracy for MPE than pADA. However, addressing these questions would require a large scale study with an adequate sample size and additional subgroup analysis. Finally, the predictive score developed in this study, incorporating clinical, radiologic and CR parameters, could enhance the accuracy of MPE diagnosis (AUC = 0.94), aligning with findings from related studies.[19, 20]

This study's strength was its prospective data collection, helping to mitigate the occurrence of missing data. Moreover, the study focused on patients with an exudative lymphocytic profile in their pleural fluid. It reflected a practical approach in real-life clinical settings before considering pADA, cytology or histopathology tests to distinguish among MPE, TPE or other nonMPE conditions. Additionally, all patients in this study underwent cytology or histopathology tests, serving as standard reference tests for discriminating between MPE and nonMPE cases. However, acknowledging certain limitations is essentially required. These included the relatively small sample size and the study's confinement to a single center, restricting the generalizability of the findings on the utility of CR in diagnosing MPE among Thai patients nationwide. Furthermore, external validation of the identified cut-off value of CR >10 was not performed in this study. Consequently, further investigations are warranted to validate the obtained results.

Conclusion

The CR, a predictive tool for diagnosing MPE, has shown good accuracy among Thai patients. The CR, calculated by dividing sLDH by pADA, is already included in the diagnostic evaluation for differential diagnosis and is easily accessible in all healthcare settings, allowing for early detection of the disease during the initial workup. Furthermore, integrating the Clinical-Radiological-CR model can potentially improve the accuracy of MPE diagnosis. However, external validation studies are still needed to confirm these parameters' reliability. Ultimately, the definitive diagnosis of MPE relies on cytology and/or histopathology examinations to determine the specific cancer subtype, which then informs subsequent treatment planning.

Conflicts of interest

We declare we have no conflicts of interest related to the research study. None of the authors had personal or professional relationships that could have influenced the study's outcome or introduced bias in interpreting the results.

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INCIDENCE AND RISK FACTORS OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) AMONG PEDIATRIC PATIENTS RECEIVING CARE IN A TERTIARY HOSPITAL IN CENTRAL THAILAND

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Abstract

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) involves severe complications after contracting SARS-CoV-2. Nevertheless, limited evidence is available of MIS-C incidence in Thailand. Therefore, the present study aimed to determine MIS-C incidence and its risk factors among Thai children.

Methods: A retrospective cohort study was conducted between 2020 and 2021. The data were obtained from medical records of pediatric patients under 15 years receiving a diagnosis of SARS-CoV-2 and obtaining treatment at Ananda Mahidol Hospital, Lopburi Province, central Thailand. The World Health Organization defined MIS-C incidence as occurring within eight weeks after contracting SARS-CoV-2. A multivariable Cox proportional hazard regression model was used for estimating the adjusted hazard ratio (AHR) and 95% confidence interval (CI) for factors associated with MIS-C.

Results: Three thousand pediatric patients with a history of SARS-CoV-2 were included in the present study. The majority (51%) were males. The median time of follow-up was 56 days. Twenty-five patients (0.83%) developed MIS-C, representing an incidence rate of 14.95 (95% CI: 9.67–22.07) per 100,000 person-days. The incidence rates among males and females were 18.77 (95% CI: 10.73–30.49) and 10.97 (95% CI: 5.02–20.83) per 100,000 person-days, respectively (p-value = 0.192). After adjusting for potential confounders, independent risk factors for MIS-C included a history of asthma (AHR: 7.65; 95% CI: 1.69–34.67), history of allergic rhinitis (AHR: 15.71; 95% CI: 5.73–43.05), history of nephrotic syndrome (AHR: 49.6; 95% CI: 5.89–417.06), every 10 mg/dL increase of C-reactive protein (AHR: 1.71; 95% CI: 1.28–2.29) and having COVID-19-related symptoms involving at least two systems (AHR: 9.36; 95%CI: 2.2–39.78) compared with those involving less than two systems.

Conclusion: A modest incidence of MIS-C was estimated among Thai children, while a higher incidence of MIS-C among male patients was observed. Factors associated with MIS-C included underlying diseases and elevated C-reactive protein levels in SARS-CoV-2.

Keywords: MIS-C, SARS-CoV-2, C-Reactive Protein, Thailand

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Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory communicable disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] It can occur at any age and often involves severe symptoms among the elderly and people with congenital diseases from a widespread worldwide outbreak, resulting in many hospitalized patients and deaths(1). Among pediatric patients, COVID-19 is often asymptomatic, alternatively producing mild symptoms compared with adults. After the first widespread outbreak in 2020, reports of MIS emerged, similar to Kawasaki disease in a severe form following SARS-CoV-2.[2]

The World Health Organization (WHO)[1] defined MIS as a multisystem inflammatory condition among children and adolescents temporally related to COVID-19.[2] The US Centers for Disease Control and Prevention (CDC) defined it as MIS-C[3], and the UK Royal College of Pediatrics and Child Health named it Pediatric MIS associated with Coronavirus Disease 2019 (PIMS-TS or PIMS)[4]. MIS-C involves severe complications after contracting SARS-CoV-2, starting when recovering from the disease or two to six weeks after contracting. The condition is primarily found among pediatric patients with a history of mild or showing no symptoms of COVID-19. The average age of children experiencing the condition was 9.7 years, and was found among boys more than among girls.[5] Signs and symptoms include fever, inflammation, systemic deterioration or shock. Like Kawasaki disease, fever, rash, red eyes, swollen hands and feet, dried cracked lips and enlarged lymph nodes are also included. Other signs include nervous system symptoms, blood circulation failure, impaired cardiac function, cytokine storm, macrophage activation syndrome, thrombosis and pulmonary embolism.[6]

More symptoms include myocarditis, which is more likely to develop as a shock and more severe signs include rapidly deteriorating gastrointestinal symptoms, acute renal failure and subsequent death.[6] Therefore, MIS-C among pediatric patients involves severe signs and symptoms that may cause disability and death.

In the US, MIS incidence among patients under 21 years and previously tested positive for SARS-CoV-2 was approximately 1 in 3,000 to 4,000 (5.1 cases per 1,000,000 monthly cases of that age group).[3, 7] MIS-C incidence was higher among Hispanics, Blacks, and Asians or Pacific Islanders compared with Whites. Furthermore, younger individuals revealed higher MIS-C incidence than older individuals. [7]

In Thailand since 2020, COVID-19 has also been a significant public health problem affecting the Thai population at every age.[8] However, epidemiologic information on MIS-C remains scarce, especially among pediatric patients. Therefore, the present study aimed to estimate the MIS-C incidence among Thai pediatric patients with a history of SARS-CoV-2 and determine factors associated with MIS-C incidence in this population.

Methods

Ethics Considerations

The study was reviewed and approved by the Institutional Review Board, Royal Thai Army Medical Department (IRBRTA), Bangkok, Thailand (approval number S039h/65), in compliance with international guidelines such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH—GCP) (approval number S040h/65). Regarding the secondary data used, the IRBRTA granted a waiver of informed consent.

Study Design and Subjects

A retrospective cohort study was conducted at Ananda Mahidol Hospital, a tertiary hospital in Lopburi Province, central Thailand. The criteria of eligible participants comprised pediatric patients under 15 years receiving a diagnosis of SAR-CoV-2 at Ananda Mahidol Hospital between January 1, 2020, and December 31, 2021. SAR-CoV-2 confirmation included (1) a positive result of SARS-CoV-2 Real-Time Polymerase Chain Reaction, (2) a positive result

of SARS-CoV-2 serology test, or (3) a positive result of SARS-CoV-2 antigen test.

Data Collection

In the current study, 3,000 pediatric patients with a history of SARS-CoV-2 were enrolled. Patient information was reviewed and retrieved by a pediatrician. A standard case report form was used to collect baseline data of individuals from medical records including demographic characteristics, comorbidity, clinical symptoms and laboratory testing at the date of diagnosis of SARS-CoV-2. The recommendation of the CDC and WHO diagnosis guidelines defined the MIS-C diagnosis.

Guidelines for diagnosing MIS-C, as recommended by the CDC and WHO, include patients with fever ≥38°C for 24 hours with at least two or more systemic symptoms:

1) rash, red eyes or inflammation of the mucous membranes; 2) low blood pressure or shock; 3) symptoms of the cardiovascular system; 4) bleeding easily due to abnormal blood clotting; 5) gastrointestinal symptoms; 6) respiratory symptoms; 7) neurological symptoms and 8) sudden renal failure. Additionally, a blood test was used showing inflammation in at least one of the following criteria: 1) C-reactive protein (CRP) >5 mg/dl, 2) D-dimer >2 mg/l, 3) erythrocyte sedimentation rate (ESR) >40 mm/hr, 4) fibrinogen >400 mg/dl, 5) ferritin >500 micrograms/ml, 6) hypoalbuminemia (<3 g/dl), 7) IL-6 >1.8 pg/ml, 8) lymphopenia (ALC <1000 cells/m^3), 9) LDH >280 U/L, 10) neutrophilia (ANC >7,700 cells/m^3) and 11) procalcitonin >0.05 ng/ml. Moreover, no other cause indicated similar symptoms including toxic shock syndrome or staphylococcal scalded skin syndrome.

Statistical Analysis

All analyses were conducted using Stata Corp., 2021, *Stata Statistical Software: Release 17*, College Station, TX, USA: Stata Corp. LLC. Baseline characteristics were analyzed using descriptive statistics. Continuous data were presented as mean and standard deviation (SD), while categorical data were presented as percentages. The person-time of observation was calculated for each participant as the duration between the participant's baseline data and the day MIS-C occurred. Those remaining patients without MIS-C were right-censored on the 56th day after the date of SAR-CoV-2 diagnosis. The incidence rates of MIS-C were calculated with 95% confidence intervals (CI) per 100,000 person-days of observation. The Kaplan–Meier estimator was used to compute survival patterns. The log-rank test was used to compare survival between males and females, while Cox proportional regression analysis was used to determine factors associated with MIS-C. Multivariable analysis was performed to estimate adjusted hazard ratios (AHR) and presented with a 95% CI. A two-sided *p*-value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 presents the baseline demographic and clinical characteristics of 3,000 pediatric patients with a history of SAR-CoV-2 included in the study. Of all participants, the majority (51%) were males. The average age of the study participants was 7.4±4.2 years. Fifty-one individuals (1.7%) presented a history of asthma, while 52 individuals (1.7%) possessed a history of allergic rhinitis. The most prevalent clinical presentation of SAR-CoV-2 was respiratory symptoms and fever, accounting for 70.1 and 59.6%, respectively. 90.1% of patients received care as outpatient treatment. Regarding laboratory testing at baseline, the average CRP was 51.0±20.3 mg/dl, while the average ESR was 57.3±12.2. The average aminotransferase level was 47.0±8.8 U/L and 29.7±9.7 U/L for aspartate and alanine transaminase, respectively.

Incidence of MIS-C among Patients with SARS-CoV-2

The median time of follow-up was three months. **Table 2** presents the incidence rate of MIS-C among patients with SARS-CoV-2. Twenty-five patients (0.83%) developed MIS-C, representing an incidence rate of 15.0 (95% CI: 9.7 to 22.1) per 100,000 person-days. **Figure 1** illustrates the Kaplan–Meier graph of MIS-C. Among patients developing MIS-C, the median

age was 7.1 years, and 64% were males. The MIS-C incident rate was 18.8 (95% CI: 10.7 to 30.5) per 100,000 person-days among males, whereas 11.0 (95% CI: 5.0 to 20.8) per 100,000 person-days among females. **Figure 2** illustrates the Kaplan–Meier graph of MIS-C by sex (p = 0.192).

Table 1. Baseline characteristics of study participants

Characteristics	n (%)
Sex	
Female	1469 (49.0)
Male	1531 (51.0)
Age (years)	
<6	1060 (35.3)
6 to 10	1041 (34.7)
11 to 15	899 (30.0)
mean ± SD	7.4 ±4.2
median (Q1-Q3)	7.1 (3.8-11.0)
Underlying diseases	
G-6PD	8 (0.3)
Asthma	51 (1.7)
Allergic Rhinitis	52 (1.7)
Congenital Heart disease	7 (0.2)
Thalassemia	15 (0.5)
Autistic	5 (0.2)
Nephrotic syndrome	7 (0.2)
Sinusitis	3 (0.1)
History of hospital admission due to COVID-19	
No	2702 (90.1)
Admit	298 (9.9)
Contact	
Family	2990 (99.7)
School	10 (0.2)
Clinical symptoms at baseline	
Fever	1788 (59.6)
Skin	18 (0.6)
Cardiovascular system	0 (0)
Hematology	0 (0)
Gastrointestinal system	192 (6.4)
Respiratory system	2103 (70.1)
Neurological system	147 (4.9)
Overall No. of symptoms at baseline	
<2	1425 (47.5)
≥2	1575 (52.5)
Laboratory test results at baseline	

Table 1. Baseline characteristics of study participants (Cont.)

Characteristics	n (%)
CRP (mg/dl)	
mean ± SD	51.0±20.3
median (Q1-Q3)	53.0 (36.5-68.0)
ESR (mm/hr)	
mean ± SD	57.3±12.2
median (Q1-Q3)	57.0 (47.0-67.0)
LDH (U/L)	
mean ± SD	69.9±7.1
median (Q1-Q3)	70.0 (64.0-76.0)
White Blood Cell (x10^3 cell/m^3)	
mean ± SD	6.1±1.7
median (Q1-Q3)	6.0 (4.5-7.5)
Absolute neutrophil count (cell/m^3)	
mean ± SD	2482.7±1061.9
median (Q1-Q3)	2366.1 (1822.1-3040.6)
Absolute lymphocyte (cell/m^3)	
mean ± SD	2012.9±862.3
median (Q1-Q3)	1856.3 (1420.0-2506.2)
Hematocrit (volume%)	
mean ± SD	34.9±4.2
median (Q1-Q3)	35.7 (32.0-38.0)
Hemoglobin (g/dl)	
mean ± SD	11.8±1.2
median (Q1-Q3)	12.0 (11.0-13.0)
Platelet (x 10^3 cell/m^3)	
mean ± SD	308.7±512.8
median (Q1-Q3)	303.8 (270.4-346.7)
Albumin (g/dl)	
mean ± SD	3.3±0.9
median (Q1-Q3)	3.0 (2.0-4.0)
AST (U/L)	
mean ± SD	47.0±8.8
median (Q1-Q3)	47.0 (42.0-54.0)
ALT (U/L)	
mean ± SD	29.7±9.7
median (Q1-Q3)	30.0 (23.0-37.0)

G-6PD: Glucose-6-phosphate dehydrogenase deficiency, COVID-19: Coronavirus 19 disease, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

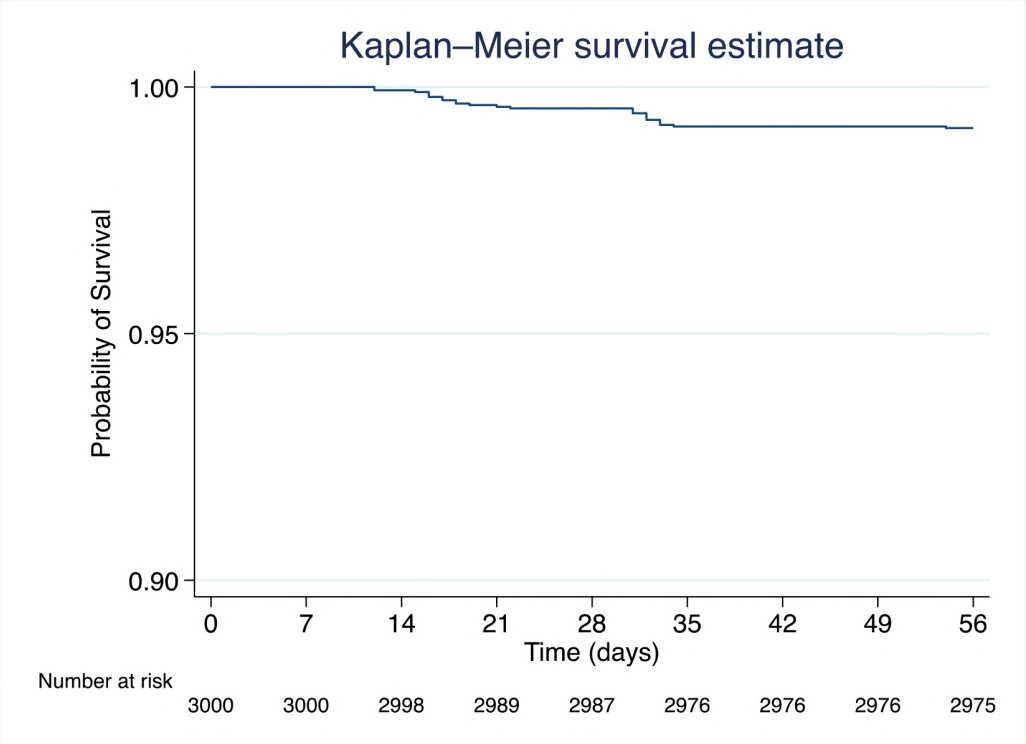

Figure 1. Kaplan–Meier Survival Graph of Multisystem Inflammatory Syndrome in Children

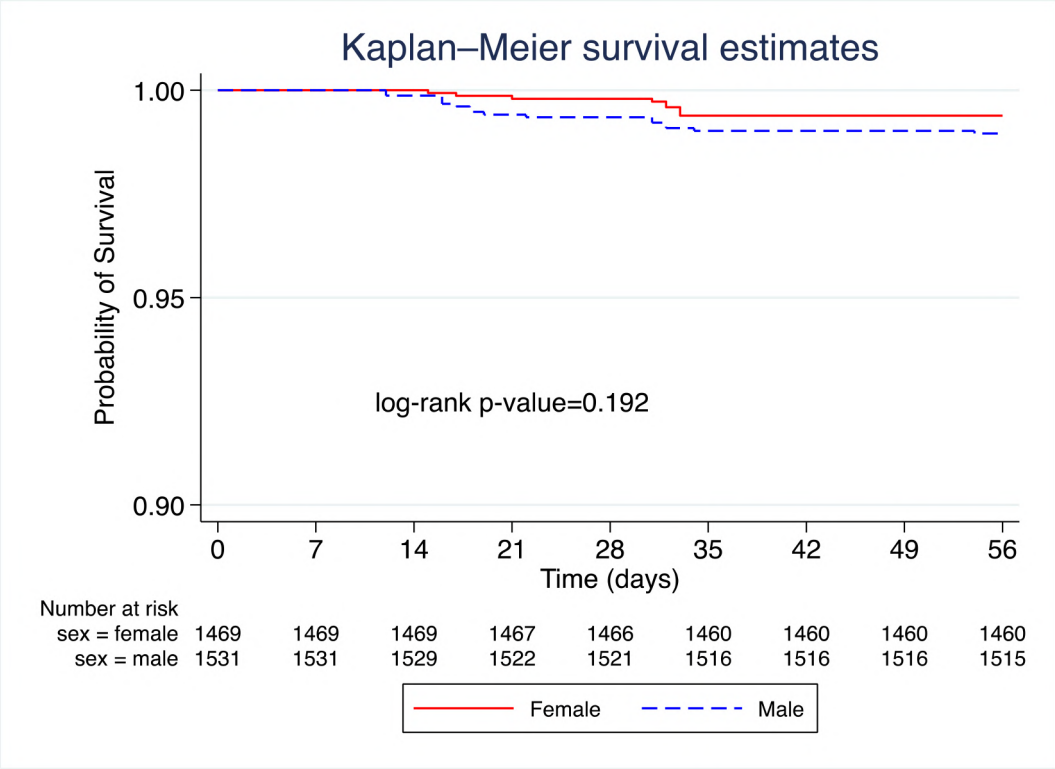

Figure 2. Kaplan–Meier survival graph of Multisystem Inflammatory Syndrome in Children by sex

Table 2. Incidence of Multisystem Inflammatory Syndrome among Children

Characteristics	Total Number	Number of MIS-C (%)	Person-days of observation	Incidence rate per 100,000 person-days (95% CI)
Overall	**3000**	**25 (0.83)**	167227	14.95 (9.67-22.07)
Sex				
Female	1469	9 (0.61)	82007	10.97 (5.02-20.83)
Male	1531	16 (1.05)	85220	18.77 (10.73-30.49)
Age (years)				
<6	1060	9 (0.85)	59085	15.23 (6.97-28.92)
6 to 10	1041	11 (1.06)	57938	18.99 (9.48-33.97)
11 to 15	899	5 (0.56)	50204	9.96 (3.23-23.24)
History of Admission due to COVID-19 infection				
No	2702	24 (0.89)	150583	15.94 (10.21-23.71)
Yes	298	1 (0.34)	16644	6.01 (0.15-33.48)

MIS-C: Multisystem Inflammatory Syndrome in Children, CI: Confidence interval

Risk Factors of MIS-C among Patients with SARS-CoV-2

Univariable Cox regression analysis for risk factors of MIS-C was performed and is presented in **Table 3**. The independent risk factors for MIS-C among patients with SARS-CoV-2 are shown in **Table 4**. After adjusting for confounders, the risk factors of MIS-C included a history of asthma (AHR: 7.7; 95% CI: 1.7 to 34.7), a history of allergic rhinitis (AHR: 15.7; 95% CI: 5.7 to 43.1), a history of nephrotic syndrome (AHR: 49.6; 95% CI: 5.9 to 417.1), every 10 mg/dL increase of CRP (AHR: 1.7; 95% CI: 1.3 to 2.3) and having COVID-19 related symptoms in at least two systems (AHR: 9.4; 95% CI: 2.2 to 39.8) compared with those in less than two systems.

Table 3. Univariable Cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children

Factors	No MIS-C	MIS-C	Univariable analysis		
	n (%)	n (%)	Unadjusted HR	95% CI	*p*-value
Sex					
Female	1460 (99.4)	9 (0.6)	1		
Male	1515 (99.0)	16 (1.1)	1.71	0.76-3.87	0.197
Age (years)					
mean ± SD	7.4 ± 4.3	6.8 ± 3.7	0.97	0.89-1.07	0.539
<6	1051 (99.2)	9 (0.85)	1		
6 to 10	1030 (98.9)	11 (1.1)	1.25	0.52-3.01	0.625
11 to 15	894 (99.4)	5 (0.6)	0.65	0.22-1.95	0.446
History of Admission					
Outpatients	2678 (99.1)	24 (0.9)	1		
Admitted	297 (99.7)	1 (0.3)	0.38	0.05-2.79	0.34
Asthma					
No	2926 (99.2)	23 (0.8)	1		
Yes	49 (96.1)	2 (3.9)	5.17	1.22-21.91	0.026

Table 3. Univariable Cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children (Cont.)

Factors	No MIS-C	MIS-C	Univariable analysis		
	n (%)	n (%)	Unadjusted HR	95% CI	*p*-value
Allergic Rhinitis					
No	2928 (99.3)	20 (0.7)	1		
Yes	47 (90.4)	5 (9.6)	14.78	5.55-39.38	<0.001
Nephrotic syndrome					
No	2969 (99.2)	24 (0.8)	1		
Yes	6 (85.7)	1 (14.3)	20.31	2.75-150.14	0.003
No. of symptoms at baseline					
<2	1423 (99.9)	2 (0.14)			
≥2	91552 (98.5)	23 (1.5)	10.46	2.47-44.36	0.001
CRP (mg/dl)					
mean ± SD	50.9 ± 20.3	67.0 ± 10.2	1.05	1.02-1.08	<0.0001
ESR (mm/hr)					
mean ± SD	57.3 ± 12.2	59.8 ± 13.1	1.02	0.98-1.05	0.311
LDH (U/L)					
mean ± SD	69.9 ± 7.12	70.0 ± 7.4	1.00	0.95-1.06	0.957
White Blood cell					
mean ± SD (x10^3 cell/m^3)	6.1 ± 1.8	6.8 ± 1.8	1.0002	1.0001-1.0004	0.047
Absolute neutrophil count					
mean ± SD (x10^3 cell/m^3)	3.0 ± 1.1	2.7 ± 0.9	1.0001	0.99-1.0004	0.343
Absolute lymphocyte count					
mean ± SD (x10^3 cell/m^3)	2.0 ± 0.9	2.2 ± 1.1	1.0002	0.99-1.001	0.359
Hemoglobin (g/dl)					
mean ± SD	11.8 ± 1.2	12.0 ± 1.0	1.14	0.82-1.60	0.437
Hematocrit (volume%)					
mean ± SD	34.9 ± 4.2	34.9 ± 4.1	0.99	0.91-1.10	0.978
Platelet					
mean ± SD (x10^3 cell/m^3)	308.6 ± 51.3	311.9 ± 48.3	1.00	0.99-1.00	0.755
Albumin (g/dl)					
mean ± SD	3.3 ± 0.9	3.5 ± 0.8	1.30	0.83-2.03	0.240
AST (U/L)					
mean ± SD	47.0 ± 8.8	49.8 ± 7.4	1.04	0.98-1.09	0.121
ALT (U/L)					
mean ± SD	29.7 ± 9.7	32.4 ± 6.0	1.03	0.98-1.07	0.173

MIS-C: Multisystem Inflammatory Syndrome in Children, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HR: Hazard ratio**,** CI: Confidence interval

Table 4. Multivariable cox regression analysis for risk factors of Multisystem Inflammatory Syndrome among Children

Factors	Adjusted HR	95% CI	*p*-value
Sex			
Female	1		
Male	1.65	0.70-3.92	0.255
Age (years)	0.94	0.85-1.05	0.266
Asthma			
No	1		
Yes	7.65	1.69-34.67	0.008
Allergic Rhinitis			
No	1		
Yes	15.71	5.73-43.05	<0.001
Nephrotic syndrome			
No	1		
Yes	49.55	5.89-417.06	<0.001
No. of COVID-19 symptoms at baseline			
Less than two symptoms	1		
At least two symptoms	9.36	2.20-39.78	0.002
CRP (every 10 mg/dL increase)	1.71	1.28-2.29	<0.001
AST (every 10 unit/L increase)	1.25	0.77-2.03	0.371

*Adjusted for sex, age, asthma, allergic rhinitis, nephrotic syndrome, number of clinical symptoms at baseline, CRP, and AST, COVID-19: Coronavirus 19 disease, CRP: C-reactive protein, AST: Aspartate aminotransferase, HR: Hazard ratio, CI: Confidence interval

Discussion

The present study provides essential evidence concerning MIS-C incidence and related risk factors among Thai pediatric patients. A higher incidence of MIS-C was observed among male patients. The corresponding risk factors for MIS-C included a history of asthma, allergic rhinitis, nephrotic syndrome, more elevated CRP and COVID-19-related symptoms in two or more systems.

Patients with MIS-C in the current study exhibited similar characteristics to those reported in the US and Europe. The median age at onset was 7.3 to 10 years, and 59% were males.[9] We found that the overall incidence rate of MIS-C among Thai pediatric patients was 15.0 per 100,000 person-days, approximately 0.8%. This rate is relatively high compared with related studies in other countries. For instance, it approximated 0.002% of US children under 21 years[7], 0.003% among children under 18 years in Italy[10] and 0.01% among children under 19 years in Sweden.[11] Our study included pediatric patients under 15 years. Thus, this may explain our finding, which is supported by the evidence of a higher incidence of MIS-C among younger children under 15 years compared with that of those over 15 years. [11]

Regarding sex, we found that the incidence of MIS-C among males was higher than that among females, consistent with related reports in the US[7] and Sweden.[11] This finding may be explained by the biological differences (genetic and epigenetic) between males and females, which may impact the immune response to SARS-CoV-2.[12] We also found a lower MIS-C incidence among patients older than 11 years compared with younger patients. These findings are compatible with the related studies, reporting that higher-aged individuals exhibit a lower incidence of MIS-C. [7, 11]

We demonstrated that MIS-C incidence among patients with asthma was 7.5 times that of those without asthma. However, the estimated AHR could have been more precise. This finding agrees with that of the related study in Sweden, demonstrating the association between asthma and MIS-C among children.[11] Asthma results in dysregulation in the immune system, making fighting viral infections harder.[13, 14] Furthermore, the related study indicated that the rate of COVID-19 hospital admission was higher among children with asthma than those without asthma.[15]

Additionally, we also demonstrated that allergic rhinitis was associated with MIS-C incidence. Although pathophysiology-linked allergic rhinitis and MIS-C incidence were unclear, one recent report showed that children diagnosed with MIS-C had a history of allergic rhinitis.[16] The mechanism of allergic rhinitis involves the emergence of anti-IgE antibody and specific antibodies to cytokines correlating to allergic inflammation.[17] Therefore, this may link to MIS-C through the inflammatory pathway.

We explored that pediatric patients with nephrotic syndrome tended to have a higher incidence of MIS-C than those without. Although the estimated AHR for the association between those was imprecise, this finding may be explained by the fact that patients with nephrotic syndrome are prone to acute kidney injuries linked to MIS-C.[3, 18] Furthermore, we reported that MIS-C incidence among patients with two or more clinical symptoms of COVID-19 tended to be higher than those with less than two clinical symptoms of COVID-19. Therefore, our findings suggest that pediatric patients with comorbidities having SAR-CoV-2 and presenting more clinical symptoms of COVID-19 should be closely monitored for MIS-C at least within eight weeks after the onset of COVID-19.

Patients with MIS-C in the present study exhibited increased inflammatory markers, especially CRP, which was also reported in other MIS-C cohorts in other countries.[19–23] After adjusting for potential confounders, we found that every 10 mg/dL increase of CRP tended to increase the risk for MIS-C by 71%. Moreover, our estimated AHR for the association between CRP and MIS-C was relatively precise (95% CI: 1.28–2.29). High CRP level associated with MIS-C, like the proinflammatory effect of SARS-CoV-2 infection, has been reported among adults with severe COVID-19, with whom MIS-C shares some characteristics including dysregulated innate immune response and cytokine storm.[22, 23] This issue may be a key point for monitoring MIS-C among patients with COVID-19 with high CRP values.

The present study encountered several limitations. First, the study included only pediatric patients with SAR-CoV-2 receiving care in one tertiary hospital in central Thailand; therefore, the generalizability is limited. Second, we included participants under 15 years; thus, we did not have the opportunity to assess the MIS-C incidence among children and adolescents of older age. Third, regarding the power of the study, the estimated AHR for the risk factors for MIS-C may not have been relatively precise. However, the present study constituted an early study providing epidemiologic data on MIS-C among pediatric patients in Thailand. Understanding SARS-CoV-2 transmission among children and its short term consequences is essential. Reinforcing the need for long term multidisciplinary follow-up is crucial because whether these patients will experience a chronic impairment or other sequelae remains unknown.

Conclusion

A modest incidence of MIS-C was estimated among Thai children, while a higher incidence of MIS-C among male patients was observed. Factors associated with MIS-C were underlying diseases including a history of asthma, allergic rhinitis, nephrotic syndrome, COVID-19-related symptoms in two or more systems and high C-reactive protein levels in SARS-CoV-2.

Availability of data and materials

The datasets generated or analyzed during the current study are not publicly available because they contain sensitive identifying information. Because ethics restrictions have been placed, the datasets are available from the author on

reasonable request (contact Nutthaporn Narknok via guide18cardioped@gmail.com)

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

NN and BS developed the concept for the study.

NN collected the data. BS analyzed the data.

NN and BS wrote the first draft; the authors contributed and approved the final version.

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TRENDS IN THE INCIDENCE AND CHARACTERISTICS OF CONGENITAL HEART DISEASE IN LOPBURI PROVINCE, CENTRAL THAILAND, 2017-2021

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Abstract

Background: Congenital heart disease (CHD) is the newborn's most common congenital anomaly. Nevertheless, limited evidence is available of CHD incidence in Thailand. Therefore, we aimed to determine the trends in CHD incidence from 2017 to 2021.

Methods: A descriptive epidemiology study was conducted using data from 2017-2021. We collected data from the medical records of pediatric patients with CHD at the Pediatric Cardiology Clinic at Ananda Mahidol Hospital, central Thailand. The pediatric cardiologist reviewed medical records to obtain participants' characteristics and medical data, including CHD diagnosis, sex, child order and maternal risk factors during pregnancy.

Results: In total, 27,882 live births were recorded between 2017 and 2021 in Lopburi Province, Thailand. The study included 584 pediatric patients with CHD born between 2017 and 2021. Of these, 312 (53.4%) were males, and 89 (15.2%) presented cyanotic CHD. Sex-adjusted CHD incidence was 22.4 per 1000 live-births (95% CI: 17.6-34.5) in 2017; then rose to 25.7 per 1000 live-births (95% CI 21.7-30.2) in 2019 and dropped to 15.4 per 1000 live-births (95% CI 12.1-19.3) in 2021 (*p* for trend = 0.317). Two hundred and fourteen patients (36.6%) presented a ventricular septal defect. In 2017, the proportion of patients receiving a diagnosis of CHD before one year of age was 57.7% and continuously rose to 100% in 2021 (*p*-for trend <0.001). The proportion of alcohol consumption during pregnancy was consistently high, ranging from 61.6 to 74.8% (*p* for trend = 0.189). In addition, contraindicated drug use during the first trimester of pregnancy was also constantly high (73.1%) among study participants over five years (*p* for trend = 0.235).

Conclusion: CHD incidence in Lopburi Province has been persistently high from 2017 to 2021. The average age at diagnosis with CHD in this study population continuously declined over five years. Characteristics of CHD risk factors during pregnancy constituted a constantly high proportion among these study participants over one half decade.

Keywords: Congenital heart disease, Incidence, Maternal risk factors, Thailand, Trend

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Introduction

Congenital heart disease (CHD) is a newborn's most common congenital anomaly.[1, 2] Global CHD incidence was estimated at 17.2 per 1,000 live births in 1990 and stabilized at 17.9 per 1,000 live births in 2017. Regarding the global report 2017, CHD incidence tended to be higher among males (19.1 per 1,000 live births) than among females (16.6 per 1,000 live births).[1] CHD incidence differed in each global region; compared with a high sociodemographic index (SDI) region, the CHD incidence concerning low SDI was relatively high.[1] Regarding advances in cardiovascular medicine and cardiac surgery over the past decade [3], the global trends in CHD mortality continuously decreased from 1990 to 2017[1]; however, CHD remains a critical cause of morbidity and mortality from a congenital anomaly.[4, 5]

In Thailand, a related study in 2009 reported data on the prevalence of CHD among school children. For instance, a related study in western Thailand reported a CHD prevalence of 1.05 per 1000 children[6], while in 2010, another study in lower north Thailand showed a CHD prevalence of approximately 0.06 per 1000 healthy school children.[7] No evidence of CHD incidence in Thailand is available. Furthermore, maternal risk factors associated with CHD[8–10], including smoking, alcohol consumption and contraindicated drug use during pregnancy, were documented in related studies.[11–13] Therefore, understanding the epidemiology of CHD incidence and knowing the trends of the disease burden of CHD are essential for planning policies and managing CHD in the context of the Thai healthcare system, which has implemented universal health coverage (UHC) since 2002.[14]

In the present study, we aimed to determine the trends in CHD incidence from 2017 to 2021 in Lopburi Province, central Thailand. Furthermore, we also explored the characteristics of pediatric patients with CHD in this study area over five years.

Methods

Ethics approval and consent to participate

The study was reviewed and approved by the Institutional Review Board, RTA Medical Department, Bangkok, Thailand, in compliance with international guidelines such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice (ICH—GCP) (approval number S040h/65). Because we used secondary data, the Institutional Review Board, RTA Medical Department granted a waiver of informed consent.

Study design and subjects

A descriptive epidemiology study was conducted using data from medical records from 2017 to 2021. We retrieved the data from the Pediatric Cardiology Clinic at Ananda Mahidol Hospital, a tertiary hospital in Lopburi Province. Since 2017, Lopburi Province has had only one pediatric cardiologist (N.N.) at Ananda Mahidol Hospital. Regarding the UHC scheme implemented in Thailand since 2002 [14, 15], all children who had been examined and were patients with suspected CHD from all hospitals in different areas of Lopburi Province would be directed through the coordination center and referred to the Pediatric Cardiology Clinic at Ananda Mahidol Hospital. Typically, clinically screened newborns by physical examination and measuring the oxygen saturation in the hands and feet were performed. [15] Then pediatric patients with suspected CHD would be referred to the Pediatric Cardiology Clinic for a definite diagnosis. All pediatric patients with suspected CHD would be physically examined and investigated at the Pediatric Cardiology Clinic; the pediatric cardiologist (N.N.) would make a definite diagnosis and collect those patients' data at the Pediatric Cardiology Clinic database.

In the present study, we intended to determine trends in CHD incidence per live birth from 2017 to 2021; therefore, the enrolled participants were pediatric patients receiving a diagnosis of

CHD and were born in Lopburi Province from January 1, 2017 to December 31, 2021. The number of live births in Lopburi Province from 2017 to 2021 was obtained from the National Statistical Office (NSO), Thailand.[16] Regarding the NSO data, the total number of live births in Lopburi Province accounted for 6353, 6007, 5486, 5299, and 4737 in 2017, 2018, 2019, 2020 and 2021, respectively.

Data collection

We collected the data from the medical records of pediatric patients with CHD at the Pediatric Cardiology Clinic, Ananda Mahidol Hospital, from 2017 to 2021. The pediatric cardiologist reviewed medical records to obtain participants' characteristics and medical data, for instance, sex, child order, maternal risk factors during pregnancy and signs and symptoms.

CHD diagnosis

We collected information on the symptoms presented to the doctor, CHD diagnosis and treatment plan. The International Statistical Classification of Disease and Related Health Problems, 10th Revision (ICD-10) defined the CHD diagnosis of pediatric patients. (**Supplementary 1**). Patients with innocent cardiac murmurs were excluded from the study.[11–13] Regarding CHD diagnosis, the pediatric cardiologist performed history taking, physical examination, a chest X-ray and electrocardiography. The gold standard for noninvasive imaging in CHD is echocardiography.[17] Based on the information of various procedures, when data were abnormal, an echocardiography examination would be performed for a definitive diagnosis of CHD. Furthermore, pediatric patients with CHD also received appropriate treatment, including medical and surgical treatment.

CHD classification

Regarding the study's aim to determine the characteristics of patients with CHD, we classified CHD lesions in two groups: cyanotic and acyanotic CHD. [22] Cyanotic heart disease is a congenital heart defect resulting when deoxygenated blood bypasses the lungs and enters the systemic circulation, or a mixture of oxygenated and deoxygenated blood enters the systemic circulation. The disease is caused by structural defects in the heart such as right-to-left shunts, bidi rectional shunts, malposition of the great arteries or any condition increasing pulmonary vascular resistance such as D-Transposition of the great arteries (D-TGA), pulmonary atresia; intact ventricular septum/with ventricular septal defect (VSD) and severe Tetralogy of Fallot, tricuspid atresia, single ventricle, double outlet right ventricle, truncus arteriosus, total anomalous pulmonary venous connection, critical pulmonary valve stenosis, hypoplastic left heart syndrome, aortic valve atresia and mitral valve atresia.

Acyanotic heart defect is one type of congenital heart defect. This condition diverts blood from the left to the right side of the heart, most often due to a structural defect in the interventricular septum. Oxyhemoglobin saturation in the patient's systemic circulation often remains at normal levels, such as atrioventricular septal defect, aortic stenosis, pulmonary stenosis, coarctation of the aorta, VSD and patent ductus arteriosus.

Maternal risk factors during pregnancy

Typically, the information on maternal antenatal care, including the history of exposure to occupational and environmental risks and contraindicated drug use, would be recorded in all pregnancy cases. Regarding a history of smoking and alcohol consumption during pregnancy, the data was recorded as yes or no. Other information including a history of exposure to occupational and environmental risks, history of contraindicated drug use, history of infection during pregnancy, and history of the underlying parental disease, would be noted in the medical records when positive findings were observed. The pediatric cardiologist reviewed and retrieved this information in medical records.

Occupations with a history or working environment characteristics of exposure to various chemicals such as pesticides and weed killers, mining dust industrial combustion, hydrocarbon

compounds and heavy metals define maternal occupational and environmental risks. [13] A history of contraindicated drug use during pregnancy included drug groups with a report from the study that could constitute a risk factor for congenital heart disease. Those drugs comprised amphetamines, cannabis and marijuana including anticonvulsant drugs, e.g., lithium and sodium valproate. Hormonal drugs included estrogen, progesterone or a combined oral contraceptive pill, isotretinoin. Antihypertensive drugs included angiotensin-converting enzyme inhibitors, beta blockers and renin-angiotensin system blockers. Nonsteroidal anti-inflammatory drugs (NSAIDs) included aspirin, ibuprofen, naproxen, diclofenac and indomethacin.[18–20]

In terms of maternal infection, we included viral infections during pregnancy in the first trimester, such as Hepatitis B virus (HBV), cytomegalovirus (CMV), herpes simplex virus (HSV) or coxsackie virus, which are diagnosed by physical examination with characteristic symptoms.[21] Parental underlying diseases included maternal diseases such as type 1 or type 2 diabetes mellitus, hypertension, CHD, diseases of connective tissue and immune deficiency and epilepsy, which by itself or having continued use of medications to treat that particular disease would have the opportunity to cause CHD in the child. In addition, information on a history of CHD among parents, which is related and unrelated to certain genetic diseases, was collected. [22]

Statistical analysis

Characteristics of participants were analyzed using descriptive statistics and presented categorical variables as percentages. Continuous variables like age were presented as mean and standard deviation (SD). The study's outcome was the cumulative CHD incidence each year from 2017 to 2021, presented as incidence per 1000 live births and 95% confidence interval (CI). Sex-adjusted CHD incidence was standardized by sex distribution of live births in the 2017 Thailand census. Sex-specific CHD incidence each year was also calculated. The *Cochran–Armitage* trend test was employed for CHD incidence to test the statistical significance of trends from 2017 to 2021. The *chi*-squared test was used to compare the different distributions of categorical data. All statistical tests were two-sided, and a *p*-value less than 0.05 was considered statistically significant. All statistics were analyzed using Stata Corp. 2021 *Stata Statistical Software: Release 17*. College Station, TX: Stata Corp LLC.

Results

Characteristics of study participants

Between 2017 and 2021, 27,882 live births were recorded in Lopburi Province, Thailand. Of those, 14,217 (51.1%) were males. The present study included 584 pediatric patients with CHD born from 2017 to 2021. In all, 312 (53.4%) were males, and 294 (50.3%) were first-child orders (**Table 1**).

Incidence of CHD in Lopburi Province, central Thailand, 2017 to 2021

Table 1 shows CHD incidence per 1000 live births from 2017 to 2021. Sex-adjusted CHD incidence was 22.4 per 1000 live-births (95% CI: 17.6 to 34.5) in 2017, then rose to 25.7 per 1000 live-births (95% CI 21.7-30.2) in 2019 and dropped to 15.4 per 1000 live-births (95% CI 12.1-19.3) in 2021 (*p* for trend = 0.317). Among males, CHD incidence was 26.3 per 1000 live births (95% CI: 21.1 to 32.4) in 2017, then dropped to 18.1 per 1000 live births (95% CI: 13.7 to 23.5) in 2018. After that, it rose to 24.5 and 23.7 per 1,000 live births in 2019 and 2020, respectively. In 2021, the CHD incidence among males declined to 16 per 1000 live births (95% CI 11.4 to 21.8), *p* for trend = 0.104 (**Figure 1**). Likewise, the CHD incidence among females also fluctuated. It totaled 18.3 per 1000 live births (13.9 to 23.6) in 2017, then rose to 26.9 per 1000 live births (21.1 to 33.8) in 2019 and dropped to 14.8 per 1000 live births (10.3 to 20.6) in 2021, *p* for trend = 0.759. However, in 2017, a significant difference was observed in CHD incidence between males and females, $p = 0.03$.

CHD diagnosis among pediatric patients with CHD in central Thailand

Table 2 shows the diagnosis of CHD from 2017 to 2021. Of 584 pediatric patients with CHD, VSD and atrial septal defect (ASD) were

Table 1. Incidence of Congenital Heart Disease/1000 live births in central Thailand from 2017 to 2021

		2017	2018	2019	2020	2021	*p* for trend
Overall							
Number of live birth	27,882	6,353	6,007	5,486	5,299	4,737	
CHD cases	584	142	103	141	125	73	
Incidence (case/1,000 live births)	20.9	22.4	17.1	25.7	23.6	15.4	0.329
95% CI	19.3-22.7	18.9-26.3	14.0-20.8	21.7-30.2	19.7-28.0	12.1-19.3	
Sex-adjusted incidence* (case/1000 live births)	20.9	22.4	17.2	25.7	23.6	15.4	0.317
95% CI	19.3-22.7	17.6-34.5	14.2-20.8	21.7-30.2	19.7-28.0	12.1-19.3	
Male							
Number of live birth	14,217	3,232	3,035	2,813	2,698	2,439	
CHD cases	312	85	55	69	64	39	
Incidence (case/1,000 live births)	21.9	26.3	8.1	24.5	23.7	16	0.104
95% CI	19.6-24.5	21.1-32.4	13.7-23.5	19.1-30.9	18.3-30.2	11.4-21.8	
Female							
Number of live-birth	13,665	3,121	2,972	2,673	2,601	2,298	
CHD cases	272	57	48	72	61	34	
Incidence (case/1,000 live births)	19.9	18.3	16.2	6.9	23.5	14.8	0.759
95% CI	17.6-22.4	13.9-23.6	11.9-21.4	21.1-33.8	18.0-30.0	10.3-20.6	
***p*-value (male vs. female)**	0.234	0.03	0.556	0.573	0.949	0.739	

***** Sex-adjusted CHD incidence was standardized by sex distribution of live births in the 2017 Thailand census

CHD = congenital heart disease

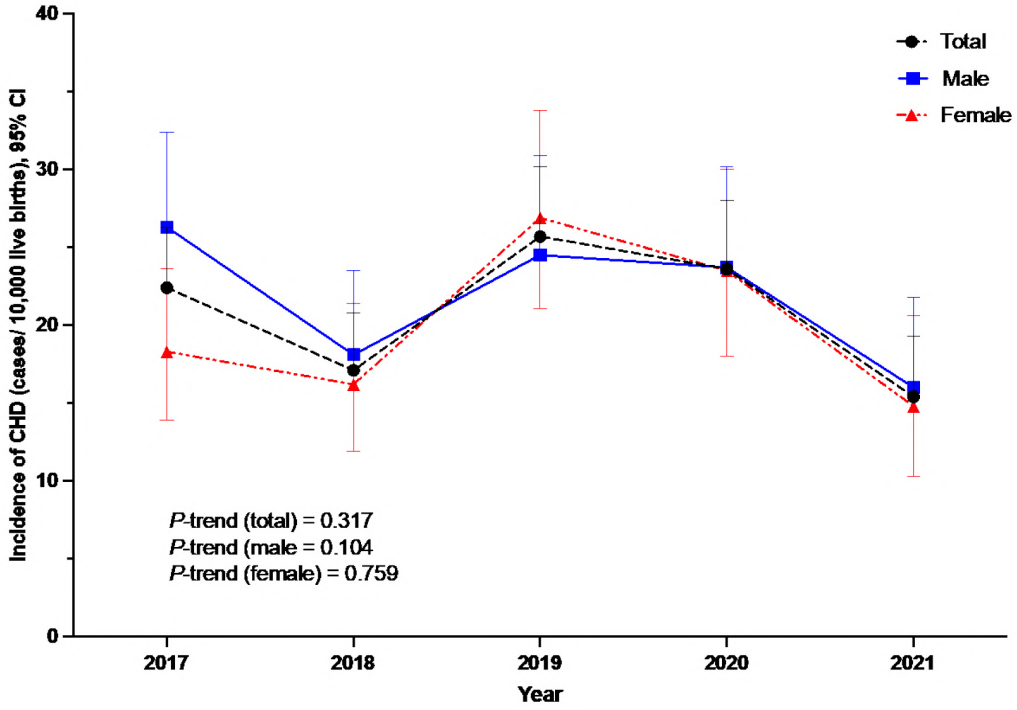

Figure 1. Incidence of Congenital Heart Disease/1000 live births (95% CI) in central Thailand from 2017 to 2021; the error bar demonstrates the 95% CI of the incidence (case/1000 live births)

the most common diagnoses among this study's participants. In all, 214 (36.6%) and 124 (21.2%) pediatric patients with CHD had VSD and ASD, respectively. At the same time, pediatric CHD patients were diagnosed with congenital pulmonary valve stenosis and patent ductus arteriosus, accounting for 11.1% and 7.5%, respectively.

Characteristics of pediatric patients with CHD in central Thailand

Table 3 shows the characteristics of pediatric patients with CHD from 2017 to 2021. The average age at diagnosis with CHD in this study population continuously decreased over five years (*p* for trend <0.001) and 69.9% of study participants received a diagnosis of CHD at <1 year old. In 2017, the proportion of pediatric patients receiving a diagnosis of CHD before one year of age totaled 57.7% and continuously rose to 61.2% in 2018, 66% in 2019, 77.6% in 2020 and 100% in 2021 (*p* for trend <0.001).

Regarding symptoms related to CHD, most pediatric patients with CHD presented cardiac murmur, accounting for 92% over five years. Furthermore, 78.3% of study participants presented growth delay. In all, 84.8% of pediatric patients with CHD exhibited acyanosis. In this group of patients, all individuals reported experiencing palpitations and dyspnea, followed by lower respiratory tract infections (90.8%), cardiac murmurs (85.1%) and growth delays (84.7%) (**Table 4**).

Regarding surgical or interventional treatment, 392 (76.1%) pediatric patients with CHD received surgical or interventional treatment. With CHD classification, pediatric patients with acyanotic CHD received definitive or palliative surgical or interventional treatment, accounting for 82.1%, while 17.9% of those with cyanotic CHD received surgical or interventional treatment (**Table 4**).

Characteristics of CHD risk factors during pregnancy

Risk factors for CHD during pregnancy among this study's participants are presented in **Table 3.** From 2017 to 2021, the proportion of maternal alcohol consumption during pregnancy

Table 2. CHD diagnosis among pediatric patients with CHD in central Thailand, from 2017 to 2021

Congenital Heart Disease (CHD)	n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)
Total	**584**	**142**	**103**	**141**	**125**	**73**
Diagnosis						
Ventricular septal defect	214 (36.6)	56 (39.4)	40 (38.8)	57 (40.4)	41 (32.8)	20 (27.4)
Atrial septal defect	124 (21.2)	21 (14.8)	26 (25.2)	27 (19.1)	31 (24.8)	19 (26)
Congenital pulmonary valve stenosis	65 (11.1)	18 (12.7)	14 (13.6)	9 (6.4)	12 (9.6)	12 (16.4)
Patent ductus arteriosus	44 (7.5)	9 (6.3)	6 (5.8)	13 (9.2)	12 (9.6)	4 (5.5)
Tetralogy of Fallot	39 (6.7)	11 (7.7)	5 (4.9)	10 (7.1)	6 (4.8)	7 (9.6)
Atrioventricular septal defect	17 (2.9)	5 (3.5)	1 (1)	6 (4.3)	5 (4)	N/A
Double outlet right ventricle	13 (2.2)	6 (4.2)	1 (1)	4 (2.8)	N/A	2 (2.7)
Stenosis of pulmonary artery	12 (2.1)	3 (2.1)	2 (1.9)	4 (2.8)	2 (1.6)	1 (1.4)
Congenital malformation of great arteries, unspecified	10 (1.7)	1 (0.7)	2 (1.9)	3 (2.1)	4 (3.2)	N/A
Coarctation of aorta	6 (1)	1 (0.7)	2 (1.9)	N/A	2 (1.6)	1 (1.4)
Congenital stenosis of aortic valve	5 (0.9)	2 (1.4)	N/A	1 (0.7)	1 (0.8)	1 (1.4)
Pulmonary infundibular stenosis	5 (0.9)	N/A	1 (1)	1 (0.7)	1 (0.8)	2 (2.7)
Congenital insufficiency of aortic valve	4 (0.7)	1 (0.7)	1 (1)	N/A	1 (0.8)	1 (1.4)
Atresia of pulmonary artery	3 (0.5)	N/A	1 (1)	1 (0.7)	1 (0.8)	N/A
Primary pulmonary hypertension	3 (0.5)	2 (1.4)	N/A	1 (0.7)	N/A	N/A
Pulmonary valve atresia	3 (0.5)	N/A	N/A	2 (1.4)	N/A	1 (1.4)
Aortopulmonary septal defect	2 (0.3)	N/A	N/A	N/A	2 (1.6)	N/A
Congenital malformation of cardiac septum, unspecified	2 (0.3)	2 (1.4)	N/A	N/A	N/A	N/A
Dextrocardia	2 (0.3)	1 (0.7)	N/A	1 (0.7)	N/A	N/A
Mitral insufficiency	1 (0.2)	N/A	N/A	N/A	1 (0.8)	N/A
Anomalous portal venous connection	1 (0.2)	N/A	N/A	N/A	1 (0.8)	N/A

Table 2. CHD diagnosis among pediatric patients with CHD in central Thailand from 2017 to 2021 (Cont.)

Congenital Heart Disease (CHD)	n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)
Aortic (valve) insufficiency	1 (0.2)	1 (0.7)	N/A	N/A	N/A	N/A
Aortic (valve) stenosis with insufficiency	1 (0.2)	N/A	N/A	N/A	N/A	1 (1.4)
Dilated cardiomyopathy	1 (0.2)	N/A	1 (1)	N/A	N/A	N/A
Ebstein's anomaly	1 (0.2)	1 (0.7)	N/A	N/A	N/A	N/A
Mitral (valve) insufficiency	1 (0.2)	N/A	N/A	1 (0.7)	N/A	N/A
Mitral valve disease, unspecified	1 (0.2)	N/A	N/A	N/A	1 (0.8)	N/A
Non-rheumatic mitral valve disorder, unspecified	1 (0.2)	N/A	N/A	N/A	N/A	1(1.4)
Hypertrophic cardiomyopathy	1 (0.2)	1 (0.7)	N/A	N/A	N/A	N/A
Tricuspid insufficiency	1 (0.2)	N/A	N/A	N/A	1 (0.8)	N/A

CHD = congenital heart disease

Table 3. Characteristics of pediatric patients with congenital heart disease in central Thailand from 2017 to 2021

Year		2017	2018	2019	2020	2021	*p* for trend
Characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Sex							0.196
Male	312 (53.4)	85 (59.9)	55 (53.4)	69 (48.9)	64 (51.2)	39 (53.4)	
Female	272 (46.6)	57 (40.1)	48 (46.6)	72 (51.1)	61 (48.8)	34 (46.6)	
Child order							0.166
1st order	294 (50.3)	81 (57)	51 (49.5)	67 (47.5)	58 (46.4)	37 (50.7)	
2nd order	290 (49.7)	61 (43)	52 (50.5)	74 (52.5)	67 (53.6)	36 (49.3)	
Age at a definite diagnosis							<0.0001
<1 year	408 (69.9)	82 (57.7)	63 (61.2)	93 (66)	97 (77.6)	73 (100)	
≥1 years	176 (30.1)	60 (42.3)	40 (38.8)	48 (34)	28 (22.4)	0 (0)	
Mean (95% CI)	0.6 (0.5-0.7)	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.7 (0.5-0.8)	0.4 (0.3-0.6)	0 (0-0)	<0.0001
Surgical/ interventional treatment							0.323
No	192 (32.9)	39 (27.5)	38 (36.9)	49 (34.8)	39 (31.2)	27 (37)	
Yes	392 (67.1)	103 (72.5)	65 (63.1)	92 (65.2)	86 (68.8)	46 (63)	
Symptoms							
Growth delay							0.591
No	127 (21.7)	28 (19.7)	22 (21.4)	34 (24.1)	26 (20.8)	17 (23.3)	
Yes	457 (78.3)	114 (80.3)	81 (78.6)	107 (75.9)	99 (79.2)	56 (76.7)	
Lower respiratory tract infection							0.703
No	519 (88.9)	128 (90.1)	91 (88.3)	123 (87.2)	114 (91.2)	63 (86.3)	
Yes	65 (11.1)	14 (9.9)	12 (11.7)	18 (12.8)	11 (8.8)	10 (13.7)	
Murmur							0.409
No	47 (8)	8 (5.6)	9 (8.7)	13 (9.2)	11 (8.8)	6 (8.2)	
Yes	537 (92)	134 (94.4)	94 (91.3)	128 (90.8)	114 (91.2)	67 (91.8)	
Palpitation							0.464
No	582 (99.7)	142 (100)	102 (99)	141 (100)	125 (100)	72 (98.6)	
Yes	2 (0.3)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1.4)	

Table 3. Characteristics of pediatric patients with congenital heart disease in central Thailand from 2017 to 2021 (Cont.)

Year		2017	2018	2019	2020	2021	*p* for trend
Characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Chest pain							N/A
No	584 (100)	142 (100)	103 (100)	141 (100)	125 (100)	73 (100)	
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Cyanosis							0.954
No	495 (84.8)	119 (83.8)	91 (88.3)	115 (81.6)	110 (88)	60 (82.2)	
Yes	89 (15.2)	23 (16.2)	12 (11.7)	26 (18.4)	15 (12)	13 (17.8)	
Dyspnea							0.552
No	583 (99.8)	142 (100)	102 (99)	141 (100)	125 (100)	73 (100)	
Yes	1 (0.2)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	
Syncope							N/A
No	584 (100)	142 (100)	103 (100)	141 (100)	125 (100)	73 (100)	
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Risk Factors							
Infection during pregnancy							0.364
No	562 (96.2)	136 (95.8)	99 (96.1)	133 (94.3)	123 (98.4)	71 (97.3)	
Yes	22 (3.8)	6 (4.2)	4 (3.9)	8 (5.7)	2 (1.6)	2 (2.7)	
Drug use during pregnancy							0.235
No	157 (26.9)	38 (26.8)	23 (22.3)	38 (27)	31 (24.8)	27 (37)	
Yes	427 (73.1)	104 (73.2)	80 (77.7)	103 (73)	94 (75.2)	46 (63)	
Alcohol use during pregnancy							0.189
No	168 (28.8)	38 (26.8)	26 (25.2)	44 (31.2)	32 (25.6)	28 (38.4)	
Yes	416 (71.2)	104 (73.2)	77 (74.8)	97 (68.8)	93 (74.4)	45 (61.6)	

Table 3. Characteristics of pediatric patients with congenital heart disease in central Thailand from 2017 to 2021 (Cont.)

Year		2017	2018	2019	2020	2021	*p* for trend
Characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Smoking during pregnancy							0.993
No	519 (88.9)	127 (89.4)	91 (88.3)	123 (87.2)	114 (91.2)	64 (87.7)	
Yes	65 (11.1)	15 (10.6)	12 (11.7)	18 (12.8)	11 (8.8)	9 (12.3)	
Occupational and environmental risks							0.819
No	121 (20.7)	28 (19.7)	20 (19.4)	34 (24.1)	23 (18.4)	16 (21.9)	
Yes	463 (79.3)	114 (80.3)	83 (80.6)	107 (75.9)	102 (81.6)	57 (78.1)	
Parents having CHD							0.184
No	579 (99.1)	141 (99.3)	103 (100)	141 (100)	122 (97.6)	72 (98.6)	
Yes	5 (0.9)	1 (0.7)	0 (0)	0 (0)	3 (2.4)	1 (1.4)	
Parents having comorbidities							0.897
No	538 (92.1)	131 (92.3)	94 (91.3)	129 (91.5)	120 (96)	64 (87.7)	
Yes	46 (7.9)	11 (7.7)	9 (8.7)	12 (8.5)	5 (4)	9 (12.3)	

CHD = congenital heart disease

Table 4. Characteristics of pediatric patients with congenital heart disease in central Thailand by cyanosis

Characteristics	**No Cyanosis n (%)**	**Cyanosis n (%)**	***p*-value**
Sex			0.413
Male	268 (85.9)	44 (14.1)	
Female	227 (83.5)	45 (16.5)	
Child order			0.783
1st order	248 (84.4)	46 (15.6)	
2nd order	247 (85.2)	43 (14.8)	
Age at a definite diagnosis			0.011
<1 year	356 (87.3)	52 (12.7)	
≥1 years	139 (79)	37 (21)	
Surgical/ interventional treatment			0.012
No	173 (90.1)	19 (9.9)	
Yes	322 (82.1)	70 (17.9)	
Symptoms			
Growth delay			0.921
No	108 (85)	19 (15)	
Yes	387 (84.7)	70 (15.3)	
Lower respiratory tract infection			0.153
No	436 (84)	83 (16)	
Yes	59 (90.8)	6 (9.2)	
Murmur			0.437
No	38 (80.9)	9 (19.1)	
Yes	457 (85.1)	80 (14.9)	
Palpitation			0.548
No	493 (84.7)	89 (15.3)	
Yes	2 (100)	0 (0)	
Chest pain			N/A
No	495 (84.8)	89 (15.2)	
Yes	0 (0)	0 (0)	
Dyspnea			0.671
No	494 (84.7)	89 (15.3)	
Yes	1 (100)	0 (0)	
Syncope			N/A
No	495 (84.8)	89 (15.2)	
Yes	0 (0)	0 (0)	
Infection during pregnancy			0.696
No	477 (84.9)	85 (15.1)	
Yes	18 (81.8)	4 (18.2)	
Drug use during pregnancy			0.81
No	134 (85.4)	23 (14.6)	
Yes	361 (84.5)	66 (15.5)	

Table 4. Characteristics of pediatric patients with congenital heart disease in central Thailand by cyanosis (Cont.)

Characteristics	No Cyanosis n (%)	Cyanosis n (%)	*p*-value
Alcohol use during pregnancy			0.878
No	143 (85.1)	25 (14.9)	
Yes	352 (84.6)	64 (15.4)	
Smoking during pregnancy			0.153
No	436 (84)	83 (16)	
Yes	59 (90.8)	6 (9.2)	
Occupational and environmental risks			0.874
No	102 (84.3)	19 (15.7)	
Yes	393 (84.9)	70 (15.1)	
Parents having CHD			0.766
No	491 (84.8)	88 (15.2)	
Yes	4 (80)	1 (20)	
Parents having comorbidities			0.39
No	454 (84.4)	84 (15.6)	
Yes	41 (89.1)	5 (10.9)	

CHD = congenital heart disease

among pediatric patients with CHD was consistently high, ranging from 61.6 to 74.8% (*p* for trend 0.189). In addition, maternal contraindicated drug use during the first-trimester pregnancy was also constantly high (73.1%) among study participants over five years (*p* for trend 0.235). Furthermore, among pediatric patients with acyanotic CHD, approximately 84% reported maternal alcohol consumption during pregnancy and contraindicated drug use (**Table 4**).

Regarding occupational and environmental risks, from 2017 to 2021, 79.3% of pediatric patients with CHD reported maternal exposure to occupational and environmental risks during pregnancy. The constantly high proportion of occupational and environmental risks over five years was also observed (*p* for trend 0.819). Among pediatric patients with acyanotic CHD, approximately 85% experienced maternal exposure to occupational and environmental risks during pregnancy (**Table 4**). For infection during pregnancy, the proportion of pediatric patients with CHD presented a maternal infection, accounting for 4.2% in 2017, and dropping to 2.7% in 2021.

Discussion

The current study successfully included 584 pediatric patients with CHD in Lopburi Province, central Thailand, from 2017 to 2021. To our knowledge, this constitutes the first and updated report on trends in CHD incidence and characteristics in Thailand. CHD incidence in the present study has been constantly high over five years. Males were more likely to have CHD than females, and VSD and ASD were the most common CHD diagnoses among study participants. The average age at diagnosis with CHD in this study population continuously decreased over five years; moreover, the proportion of pediatric patients receiving a diagnosis of CHD before one year of age significantly rose from 2017 to 2021. Characteristics of CHD risk factors during pregnancy, including alcohol consumption, contraindicated drug use and occupational and environmental risks, comprised a constantly large proportion among these study participants over one half decade.

A global report indicated that the CHD incidence rate remained stable between 1990 and 2017. [1] Likewise, our study demonstrated stable trends in CHD incidence in central Thailand from 2017 to 2020 but declined in 2021. The reduced fertility rate may explain this phenomenon with better pregnancy screening and antenatal planning during the COVID-19 pandemic. [23] Therefore, revealing the information on CHD in the long run after the COVID-19 pandemic will be necessary.

In the present study, we reported that overall CHD incidence was 20.9 per 1,000 live births, which had been constantly high between 2017 and 2021. It indicated that CHD incidence in the current study was relatively high compared with the global CHD incidence in 2017, which was estimated at 17.9 per 1,000 live births.[8] Our study indicated that CHD incidence in Thailand was far higher than in countries with a high middle sociodemographic index, reporting 11.8 CHD cases per 1,000 live births in 2017.[8] In Thailand, a few related studies reported data on the prevalence of CHD among school children and adults. For instance, a related study in Tak Province, Thailand, reported a CHD prevalence of 1.05 per 1000 elementary school children in 2009 [6], while in 2010, another study in lower northern Thailand demonstrated a prevalence of CHD of approximately 0.06 per 1000 healthy school children.[7] Furthermore, a study from a university hospital in Bangkok was conducted among adult patients, showing that the CHD prevalence between 2003 and 2013 was approximately 4%. [24] Unfortunately, the results of these studies are difficult to compare because of different study populations and designs. However, our results indicated that CHD in central Thailand remains an essential health issue among children.

Regarding characteristics of pediatric patients with CHD, our study found that CHD incidence among males was more likely than among females, which was compatible with the global report.[1] A related study also emphasized that compared with females, mortality was more significant among males with CHD.[25] In line with the related literature[7, 26], approximately 90% of CHD cases were acyanotic CHD, and VSD was the most common lesion of CHD, followed by ASD. Our findings agreed with the related evidence[7, 26] that only one tenth of CHD involved cyan is related to severe CHD; moreover, we also found that approximately one third and one fifth of study participants presented VSD and ASD, respectively.

Our results demonstrated that the average age at diagnosis with CHD constantly decreased since 2017, and in 2021, 100% of pediatric patients with CHD received a definite diagnosis before one year. This finding reflects the advantages of Thailand's health system, especially in this study area, including the universal health coverage scheme implemented since 2002, the seamless referral system, advancements in the CHD screening process and the availability of pediatric cardiologists in Lopburi Province leading to reduced waiting times for diagnosis.

Our study reported that two fifths of pediatric patients with CHD received surgical or interventional treatment regarding CHD severity. Of those receiving the surgical treatment, 17.9% were cyanotic CHD, while one to ten patients without surgical treatment had acyanotic CHD. To date, according to the advancement of treatment technology, pediatric patients with minor lesions of CHD receive the current treatment as a cardiac catheter and a closed device instead of open-heart surgery, bringing significant benefits to patients in alleviating complications after surgery and reducing hospital stays. [21, 22] On the other hand, in cases of severe symptoms, patients with CHD would be sent for open heart surgery, which could only be performed in university and regional hospitals.

Related evidence documented various maternal risk factors associated with CHD, including smoking, alcohol consumption and contraindicated drug use during pregnancy. [11–13] In the present study, we did not obtain an opportunity to measure an association between maternal risk factors during pregnancy and CHD because only CHD cases were included. However, we found a large proportion of these maternal risk factors among pediatric patients with CHD, which were constantly high over

five years. These findings may explain the high CHD incidence in this area and reflect this population's health literacy problems and health risk behaviors. Therefore, our study suggested that maternal health literacy should be improved. For instance, evidence supporting group antenatal care can improve maternal health literacy, increase healthy behaviors, improve the quality of care and improve maternal and newborn outcomes. [29]

Many industrial factories and agricultural industries are distributed in this study site; early pregnant women may be exposed to occupational and environmental risks such as chemical substances throughout their living areas or working careers, affecting the newborn's development.[12] Thus, other than improving maternal health literacy, community participation, including local authorities, employers and community members, should be aware of these health risks and collaborate to solve these health challenges. [30,31]

This study encountered several limitations. Firstly, this constituted a descriptive epidemiology study in which we collected data from the Pediatric Cardiology Clinic at Ananda Mahidol Hospital; consequently, suspected pediatric patients with CHD attending other hospitals outside Lopburi Province would be excluded from the present study. Therefore, the incidence of CHD in the present study may have been underestimated. However, regarding implementing the UHC scheme in Thailand, between 2017 and 2021, all CHD cases in Lopburi Province should have received a diagnosis at this Pediatric Cardiology Clinic. Secondly, regarding the variability of healthcare facilities in different hospitals in Lopburi Province, the screening process to detect pediatric patients with suspected CHD to receive a definite diagnosis at the Pediatric Cardiology Clinic could have underestimated CHD incidence in the present study. Thirdly, although at present, echocardiography is the gold standard for noninvasive imaging in CHD, the existing literature demonstrated that diagnostic errors in pediatric echocardiography could occur, especially among patients weighing less than 5 kg.[32] Fourthly, we lacked the opportunity to collect data on exposure among individuals without CHD; hence, in the present study, the association between exposure and incidence of CHD was not evaluated. However, we could report characteristics of CHD risk factors in only the proportion and trend of maternal risk factors among pediatric patients with CHD. Consequently, further study using a case-control design may be helpful to explore the association between exposures and CHD. Fifth, regarding the retrospective data, the information on maternal risk factors was recorded in the medical records as positive findings, and we cannot guarantee that if the information did not appear in medical records, it would remain unexposed; accordingly, misclassification may have occurred. Finally, the study was conducted in Lopburi Province, so the results may not be generalized to the whole country. However, it may reflect the actual situation in this province in central Thailand, where a pediatric cardiologist is available.

Conclusion

CHD incidence in central Thailand remained persistently high from 2017 to 2021, and VSD and ASD were the most common CHD diagnoses among study participants. The average age at diagnosis with CHD in this study population continuously declined over five years. Maternal risk factors for CHD during pregnancy including alcohol consumption, contraindicated drug use and occupational and environmental risks in the first trimester of pregnancy, revealed a constantly large proportion among these study participants.

Availability of data and materials

The datasets generated or analyzed during the current study are not publicly available; the data sets are available from the author on reasonable request (contact Nutthaporn Narknok via guide-18cardioped@gmail.com)

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

NN and BS developed the concept for the study. NN collected the data. BS analyzed the data. NN and BS wrote the first draft; all authors contributed and approved the final version.

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