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Original Article

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Calcium Distribution Patterns of the Aorta as Predictors of Significant Coronary Artery Disease in Patients with Moderate to Severe Aortic Stenosis

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ABSTRACT

OBJECTIVE Computed tomography (CT) of the aortic valve and aorta has gained a greater role in planning for aortic valve replacement (AVR). However, when AVR is planned, invasive coronary angiography remains the standard investigation. Whether the calcium distribution pattern in the aorta predicts the significant presence of coronary artery disease (CAD) in patients undergoing AVR remains unclear. This study evaluated the correlation between the calcium distribution pattern from the CT aorta to predict significant CAD in patients with symptomatic moderate to severe aortic stenosis undergoing AVR.

METHODS This retrospective study included candidates for AVR either with transcatheter replacement (TAVR) or surgical replacement (SAVR) at a single tertiary-care center between 2017 and 2022. The calcium distribution patterns from the left ventricular outflow tract up to the descending aorta were analyzed from the non-contrast CT of the aorta. Significant CAD was identified from invasive coronary angiography and was defined as 50% diameter stenosis (DS) of the left main and 70% DS of the proximal left anterior descending artery. Multivariate logistic regression analysis was performed to identify the calcification pattern associated with the significant CAD.

RESULTS In total, 110 patients were included in the analysis. Among them, 40 patients (36.4%) were candidates for TAVR, while 70 patients (63.6%) were candidates for SAVR. The prevalence of significant CAD was 12.7%. Baseline characteristics were similar between patients with and without CAD, with the exception of a higher prevalence of chronic kidney disease in the CAD group (42.9% vs. 19.8%, p = 0.01). The presence of calcium at the ostium of the coronary artery and descending aorta was an independent predictor of significant CAD (OR 3.44, 95% CI1.30-9.10, p = 0.01 and OR 12.03, 95% CI 1.14-126.84, p = 0.04).

CONCLUSIONS This pilot study showed that calcium at the ostium of the coronary artery and descending aorta from non-contrast CT aorta was associated with significant CAD in patients with moderate to severe AS. Further study with more subjects be needed to confirm the findings.

KEYWORDS calcium distributions; aortic stenosis; coronary artery disease; computed coronary angiography

INTRODUCTION

Computed tomography (CT) of the aortic valve and aorta has increasingly played a significant role in planning for aortic valve interventions. The aortic valve calcification load from CT can aid in determining the severity of aortic valve stenosis (1) and serve as a prognostic factor for survival (2) and complications related to the procedure (3, 4), especially for transcatheter aortic valve replacement (TAVR).

Presently, a dedicated CT protocol is mandatory for patients with aortic stenosis who are candidates for TAVR (5, 6). The main purpose of CT angiography for TAVR planning is to evaluate the aortic valve, annulus, vascular access routes and any potential obstacles that could affect the procedure (6, 7). It appears that CT is not limited to TAVR planning: for modern minimally invasive aortic valve surgery, CT of the aorta is also important in planning the procedure (8). The complex anatomy is associated with prolonged operation times (8).

In addition to concern about aortic valve disease, coronary artery disease (CAD) is also one of the comorbidities that influence the treatment plan. The severity of CAD can change the approach from surgical aortic valve replacement (SAVR) to TAVR or vice versa, depending on the surgical risk (6). The prevalence of CAD in patients who underwent TAVR ranged from 30.0% to 74.9% (9, 10), whereas in patients who underwent SAVR, it ranged from 48.9% to 52.2% (11, 12). According to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease, invasive coronary angiography (ICA) remains the standard investigation when aortic valve intervention is planned (6).

Concerning the fact that ICA can be costly and carries the risk of complications, there have been attempts to optimize the use of data obtained from the CT. Recently, Kondoleon and colleagues performed coronary reconstruction from the computed tomography angiography (CTA) for TAVR planning and reported that CTA could reduce the need for ICA in 51.8% of patients (13). This finding could be explained by the high negative predictive values of the CTA, which were up to 97-99% (13).

Despite the positive data supporting CTA for TAVR planning in evaluating CAD, clinical guidelines limit the use of CTA to patients who are at low risk of atherosclerosis (6). Additionally, the presence of heavy calcification of the coronary trees hampers the diagnostic accuracy of CTA (14). Our hypothesis posited that the distribution of calcium along the aorta could serve as a predictor for the presence of significant proximal CAD. In the current study, we sought to maximize the use of CT data irrespective of the procedural plan, image protocol and atherosclerotic risk in identifying patients with significant CAD before undergoing aortic intervention.

METHODS

Study design and study population

This retrospective pilot study included patients with moderate to severe aortic stenosis (defined as a mean gradient ≥ 20 mmHg, peak aortic jet velocity (Vmax) ≥ 3 m/s, or aortic valve area (AVA) ≤ 1.5 cm^2) (6) who had indications of aortic valve intervention. We excluded patients with a history of coronary artery bypass graft (CABG) and those with a history of percutaneous coronary intervention (PCI) performed more than 2 years prior. Data was collected from January 2017 to January 2022 at Maharaj Nakorn Chiang Mai Hospital. The study was granted an ethics exemption by the Institutional Review Board (study number: MED-2565-08783). Informed consent was waived as the data collection was retrospective and without patient identifiers.

CT acquisition protocol

All patients were scanned using a third-generation dual source CT scanner (SOMATOM Force, Siemens AG, Munich, Germany). A non-contrast prospective ECG-gating transaxial scan of the heart between the level of the tracheal carina and the diaphragm was performed using ultra-high-pitch spiral acquisition with a tube voltage of 120 kV and adaptive tube current. The images were reconstructed using a standard filtered-back projection algorithm with 3.0-mm slice thickness and 2.5-mm slice increment. The acquisition was from the bottom of the valve to the level of the sinotubular junction and the thoracic aorta. These regions were determined 2-dimensionally using data sets on a Syngovia workstation.

CT calcium distribution analysis

The calcium distribution patterns were analyzed offline by two interventional cardiologists (T.T. and S.D.) using the hospital picture archiving and communication system (PACS) system. Figure 1 illustrates the aortic segments being evaluated. The calcification pattern was visually assessed in five zones from the left ventricular outflow to the descending aorta as follows: zone i) left ventricular outflow, zone ii) aortic annulus to junction, zone iii) coronary ostium and ascending aorta, zone iv) aortic arch, and zone v) descending aorta. The definition of each segment of the aorta follows the aortic segmentation according to the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease (15). The presence of calcium in the aortic segments of each patient was recorded as presence or absence. There was no volumetric analysis of the calcification due to the lack of a valid method for assessing calcium at the aortic wall. All calcified plaques were identified by visual estimation. The analysts were blinded to the results of the ICA study.

Invasive coronary angiography

All patients included in the analysis underwent ICA before aortic valve intervention. The procedures were performed using 5 French diagnostic catheters with standard techniques and projection planes. The severity of stenosis was gauged by visual estimation by experienced interventional cardiologists in multiple views. Significant CAD was defined as diameter stenosis ≥ 50% for the left main coronary artery and ≥ 70% of the proximal left anterior descending artery (LAD) (16).

Statistical analysis

Descriptive analysis results are presented as frequency and percentage for qualitative data, and as mean plus standard deviation (SD) for quantitative data. For comparative analysis, Fisher's exact and Chi-square tests were used to compare discrete data, while Student's T-test was used to compare normally distributed continuous data.

The association between the calcium distribution pattern and significant left main and proximal LAD stenosis was analyzed using univariate and multivariate logistic regression analysis. The correlation is presented as an adjusted odds ratio and 95% confidence interval. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). A two-sided $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline characteristics

From January 1, 2017 through January 31, 2022, 179 patients were scheduled for aortic valve intervention and underwent ICA. Of these, 69 patients (38.5%) were excluded from the analysis due to incomplete data. Among the remaining patients, 96 (87.3%) did not have significant CAD, while 14 (12.7%) did have significant CAD. The baseline characteristics of the patients with and without significant CAD are summarized in Table 1. The baseline characteristics were not different between the two groups, with the exception that the CAD group had a higher prevalence of chronic kidney disease compared to the non-CAD group (42.9% vs. 19.8%, $p = 0.01$). In addition, mitral regurgitation was significantly more common in patients without CAD than those with CAD, with rates of 56.1% and 28.5%, respectively ($p = 0.01$). Mean aortic valve gradient was also significantly greater in patients without CAD compared to those with CAD. (53.4±22.1 vs. 38.5±14.0 mmHg, $p = 0.02$). (Table 2)

Calcium distribution pattern and predictors of significant CAD

The univariate and multivariate analysis of the calcium distribution patterns and the significant presence of CAD in the left main and proximal coronary arteries is shown in Table 3. A notable

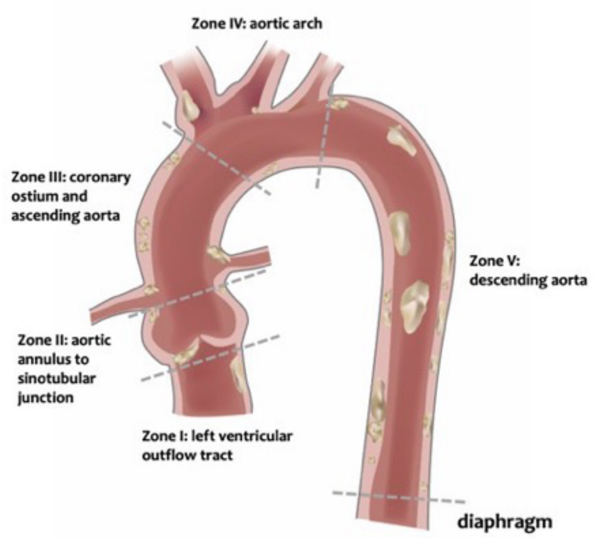

Figure 1. Assessment of the calcification pattern in the aorta

Table 1. Baseline characteristics of patients with and without CAD

Baseline characteristics	Without CAD (n=96)	CAD (n=14)	*p*-value
Age, years	71.7±9.5	71.2±14.9	0.92
Men, n (%)	49 (51.0)	8 (57.1)	0.45
Body mass index, kg/m^2	23.6±3.7	24.8±4.5	0.38
NYHA functional class, n (%)			0.29
Class I	7 (10.3)	0 (0.0)	
Class II	45 (66.2)	5 (55.6)	
Class III	13 (19.1)	4 (44.4)	
Class IV	3 (4.4)	0 (0.0	
Underlying diseases, n (%)			
Hypertension	58 (60.4)	10 (71.4)	0.56
Diabetes mellitus	28 (29.2)	7 (50.0)	0.13
Dyslipidemia	45 (46.9)	8 (57.1)	0.57
Atrial fibrillation	16 (16.7)	2 (14.3)	1.00
Cerebrovascular accident	5 (5.2)	2 (14.3)	0.22
History of heart failure	39 (40.6)	5 (35.7)	0.78
Chronic lung disease	9 (9.4)	1 (7.1)	1.00
Liver disease	2 (2.1)	0 (0.0)	1.00
Carotid artery stenosis	1 (1.0)	0 (0.0)	1.00
Chronic kidney disease			0.01
Without dialysis	10 (10.4)	6 (42.9)	
With dialysis	9 (9.4)	0 (0.0)	
Labs and Investigations			
Baseline hemoglobin, g/dL	11.9±1.9	11.9±2.7	0.94
Baseline serum creatinine, mg/dL	1.6±1.9	1.3±0.5	0.58
Baseline eGFR (CKD-EPI)	62.3±26.7	57.9±25.9	0.58
Electrocardiography			
Baseline PR interval, ms	177.8±34.7	168.2±40.1	0.45
Baseline QRS duration, ms	99.0±19.1	95.2±17.4	0.58

Data are shown as n (%) or mean±SD

CAD, coronary artery disease; CKD-EPI, CKD epidemiology collaboration; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association, QRS duration, the time it takes for an electrical impulse to travel through the ventricles of the heart; PR interval, the period, measured in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS complex

association with significant CAD was observed for calcium located at the ostial of the coronary artery (odds ratio [OR] 4.17, 95% confidence interval [CI] 1.73-10.05, $p = 0.002$) and the descending aorta (OR 11.23, 95% CI 1.40-90.38, $p = 0.01$). Calcium distribution at the origin of the coronary artery and in the descending aorta remained significantly associated with significant CAD in multivariate regression analysis (OR 3.44, 95% CI 1.30-9.10, $p = 0.01$, and OR 12.03, 95% CI 1.14-126.84, $p = 0.04$, respectively).

Comparison of characteristics of patients undergoing TAVR and SAVR

We further explored the differences in baseline characteristics between patients undergoing TAVR and those undergoing SAVR. There were 40 (36.4%) eligible candidates for TAVR and 70 (63.6%) suitable candidates for SAVR. Patients scheduled for TAVR were older than those scheduled for SAVR (79.4±6.4 years and 67.1±9.4 years, respectively, $p < 0.01$). Additionally, patients scheduled for TAVR had a higher incidence of co-morbidities than those with SAVR (Table 4).

The echocardiographic findings are shown in Table 5. The left ventricular ejection fraction (LVEF) in the TAVR group was significantly lower than that in the SAVR group (51.6±18.9% vs. 61.4±14.3%, $p = 0.01$). Remarkably, there was a distinct difference in the morphology of the aortic valve between the two groups. Trileaflet aortic valve were commonly observed in patients scheduled for TAVR (TAVR 80.0% vs. SAVR 48.6%), while bicuspid leaflets were more frequently seen in patients scheduled for SAVR (TAVR 20.0% vs. SAVR 51.4%). However, other valve pathology did not differ between the two groups of patients.

Table 2. Echocardiographic findings in patients with and without CAD

Baseline characteristics	Without CAD (n=96)	CAD (n=14)	*p*-value
Left ventricular ejection fraction (%)	57.9±16.5	56.8±19.1	0.84
Aortic valve disease etiology, n (%)			1.00
Degenerative	95 (99.0)	14 (100.0)	
Rheumatic	1 (1.0)	0 (0.0)	
Aortic valve morphology, n (%)			0.78
Trileaflet	57 (59.4)	9 (64.3)	
Bileaflet	39 (40.6)	5 (35.7)	
Aortic stenosis severity, n (%)			0.17
Moderate	4 (4.2)	2 (14.3)	
Severe	92 (95.8)	12 (85.7)	
Aortic regurgitation severity, n (%)			0.39
No	46 (47.9)	10 (71.4)	
Mild	29 (30.2)	3 (21.4)	
Moderate	19 (19.8)	1 (7.1)	
Severe	2 (2.1)	0 (0.0)	
Mitral stenosis severity, n (%)			0.52
No	93 (96.9)	13 (92.9)	
Mild	2 (2.1)	1 (7.1)	
Moderate	1 (1.0)	0 (0.0)	
Mitral regurgitation severity, n (%)			0.01
No	44 (45.8)	10 (71.4)	
Mild	32 (33.3)	2 (14.3)	
Moderate	20 (20.8)	1 (7.1)	
Severe	0 (0.0)	1 (7.1)	
Tricuspid regurgitation severity, n (%)			0.93
No	48 (50.0)	8 (57.1)	
Mild	29 (30.2)	3 (21.4)	
Moderate	13 (13.5)	2 (14.3)	
Severe	6 (6.3)	1 (7.1)	
Aortic valve area, cm^2	0.67±0.3	0.66±0.3	0.95
Mean aortic valve gradient, mmHg	53.4±22.1	38.5±14.0	0.02
Aortic valve peak velocity, m/s	4.5±0.8	4.0±0.9	0.13

Data are shown as n (%) or mean±SD
CAD, coronary artery disease

Table 3. Univariate and multivariate regression analysis of the calcium distribution pattern of predictors of significant coronary artery disease in the left main and proximal arteries

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Calcium in left ventricular outflow tract	1.44	0.45-4.60	0.570	1.79	0.44-7.35	0.420
Calcium in aortic valve annulus	-	-	0.460	-	-	-
Calcium in ostial of coronary artery	4.17	1.73-10.05	0.002	3.44	1.30-9.10	0.010
Calcium in sinus of valsalva	3.02	0.87-10.49	0.080	2.64	0.62-11.22	0.190
Calcium of sinotubular junction	0.81	0.37-1.77	0.690	0.41	0.15-1.09	0.070
Calcium in ascending aorta	1.80	0.83-3.90	0.170	1.63	0.65-4.04	0.300
Calcium in aortic arch	3.20	0.83-12.34	0.140	0.92	0.18-4.80	0.920
Calcium in descending aorta	11.23	1.40-90.38	0.010	12.03	1.14-126.84	0.040

CI, confidence interval; OR, odd ratio

Table 4. Baseline characteristics of patients undergoing TAVR and SAVR

Baseline characteristics	TAVR (n=40)	SAVR (n=70)	*p*-value
Age, years	79.4±6.4	67.1±9.4	< 0.010
Men	20 (50.0)	37 (52.9)	0.770
Body mass index, kg/m^2	23.2±4.4	24.0±3.4	0.320
NYHA functional class, n (%)			0.010
Class I	1 (3.0)	6 (13.6)	
Class II	18 (54.5)	32 (72.7)	
Class III	11 (33.3)	6 (13.6)	
Class IV	3 (9.1)	0 (0.0)	
Underlying diseases, n (%)			
Hypertension	26 (65.0)	42 (60.0)	0.600
Diabetes mellitus	14 (35.0)	21 (30.0)	0.590
Dyslipidemia	20 (50.0)	33 (47.1)	0.770
Coronary artery disease	10 (25.0)	0 (0.0)	< 0.010
Atrial fibrillation	8 (20.0)	10 (14.3)	0.440
Cerebrovascular accident	6 (15.0)	1 (1.4)	0.010
History of heart failure	27 (67.5)	17 (24.3)	< 0.010
Chronic lung disease	7 (17.5)	3 (4.3)	0.020
Liver disease	0 (0.0)	2 (2.9)	0.280
Carotid artery stenosis	1 (2.5)	0 (0.0)	0.180
Chronic kidney disease			0.010
Without dialysis	11 (27.5)	5 (7.1)	
With dialysis	4 (10.0)	5 (7.1)	
Labs and Investigations			
Baseline hemoglobin, g/dL	11.3±2.2	12.3±1.8	0.030
Baseline serum creatinine, mg/dL	1.8±1.7	1.5±1.8	0.370
Baseline eGFR (CKD-EPI)	50.8±25.4	68.4±25.1	0.001
Electrocardiography			
Baseline PR interval, ms	179.5±41.3	174.4±30.9	0.540
Baseline QRS duration, ms	99.5±20.3	98.0±18.0	0.710

Data shows n (%) or mean±SD

CKD-EPI, CKD Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement

Table 6 shows angiographic characteristics of TAVR and SAVR candidates. There were no significant differences in the number of diseased vessels, left main stenosis ≥ 50%, or proximal LAD artery stenosis ≥ 70% between the two groups. Overall, significant CAD was observed in 14 patients (12.7%). One-half of the patients in the TAVR group had significant CAD that required PCI, which was performed before TAVR in 6 patients and at the index TAVR procedure in 5 patients. Among SAVR patients, 27.5% received coronary artery bypass graft surgery in the index procedure.

Table 7 summarizes the findings of CT angiography of the aorta between the two groups. The parameters of the aortic valve annulus were well matched. The aortic valve calcium score in the SAVR group was significantly higher than that observed in the TAVR group (2,878.4±1,626.7 vs. 3,908.7±2,145.2, p = 0.04). The TAVR group had significantly higher rates of calcification than the SAVR group in almost every aortic zone, except the left ventricular outflow tract zone which was comparable between the two groups.

DISCUSSION

This study focuses on examining the correlation between calcium distribution in the adjacent areas of the aortic valve and the aorta in patients with moderate to severe aortic valve stenosis who are candidates for aortic valve implantation or replacement to determine the incidence of significant CAD. To our knowledge, the present study is the first report that illustrates a correlation between calcium distribution patterns from non-contrast CT and the presence of

Table 5. Echocardiographic findings in patients undergoing TAVR and SAVR

Baseline characteristics	TAVR (n=40)	SAVR (n=70)	*p*-value
Left ventricular ejection fraction (%)	51.6±18.9	61.4±14.3	0.010
Aortic valve disease etiology, n (%)			1.000
Degenerative	40 (100.0)	69 (98.6)	
Rheumatic	0 (0.0)	1 (1.4)	
Aortic valve morphology, n (%)			0.001
Trileaflet	32 (80.0)	34 (48.6)	
Bileaflet	8 (20.0)	36 (51.4)	
Aortic stenosis severity, n (%)			1.000
Moderate	2 (5.0)	4 (5.7)	
Severe	38 (95.0)	66 (94.3)	
Aortic regurgitation severity, n (%)			0.700
No	20 (50.0)	36 (51.4)	
Mild	13 (32.5)	19 (27.1)	
Moderate	7 (17.5)	13 (18.6)	
Severe	0 (0.0)	2 (2.9)	
Mitral stenosis severity, n (%)			0.740
No	39 (97.5)	67 (95.7)	
Mild	1 (2.5)	2 (2.9)	
Moderate	0 (0.0)	1 (1.4)	
Mitral regurgitation severity, n (%)			0.700
No	14 (35.0)	40 (57.1)	
Mild	17 (42.5)	17 (24.3)	
Moderate	8 (20.0)	13 (18.6)	
Severe	1 (2.5)	0 (0.0)	
Tricuspid regurgitation severity, n (%)			0.080
No	15 (37.5)	41 (58.6)	
Mild	13 (32.5)	19 (27.1)	
Moderate	7 (17.5)	8 (11.4)	
Severe	5 (12.5)	2 (2.9)	
Aortic valve area, cm^2	0.68±0.30	0.66±0.25	0.680
Mean aortic valve gradient, mmHg	44.3±20.5	55.9±21.4	0.010
Aortic valve peak velocity, m/s	4.0±0.9	4.6±0.8	0.010

Data shows is n (%) or mean±SD
TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement

significant CAD in moderate to severe aortic stenosis (AS) patients who underwent aortic valve (AV) interventions. Many previous studies have explored the usefulness of CT aorta in identifying significant CAD. However, it should be noted that those studies focused on the comparison between CT angiography for TAVR planning or CT coronary angiography in detecting significant CAD from ICA (13). The present analysis was conducted using the non-contrast phase CT to simplify the method. This approach made it easier to evaluate for both interventional cardiologists and cardiothoracic surgery (CVT) surgeons, especially considering that not every center has dedicated software for CT analysis.

The proportion of significant CAD in the present study was found to be 12.7%, which is similar to the previously reported rate of 11.4% (13). However, it is important to note that the previous report conducted a lesion-level analysis, whereas the present study used a patient-level analysis. Additionally, the definition of significant CAD varies across studies, e.g., encompassing criteria such as all proximal segments of epicardial arteries with 70% stenosis or 50% stenosis of the left main (13), or including only proximal LAD and left main stenosis of 70% and 50%. As a result, direct comparisons of results among the trials may be challenging.

Table 6. Angiographic findings of patients undergoing TAVR and SAVR

	Total (n=110)	TAVR (n=40)	SAVR (n=70)	*p*-value
Number of diseased vessels				0.420
Not significant	61 (55.5)	19 (47.5)	42 (60.0)	
1	18 (16.4)	8 (20.0)	10 (14.3)	
2	13 (11.8)	4 (10.0)	9 (12.9)	
3	18 (16.4)	9 (22.5)	9 (12.9)	
LM stenosis ≥ 50%	5 (4.6)	1 (2.6)	4 (5.7)	0.650
Proximal LAD stenosis ≥ 70%	10 (9.1)	4 (10.0)	6 (8.6)	1.000
Significant CAD*	14 (12.7)	5 (12.5)	9 (12.9)	1.000
Location of diseased vessel				
LAD	42 (38.2)	19 (47.5)	23 (32.9)	0.160
Proximal LAD ≥ 70%	10 (9.1)	6 (10.0)	6 (8.6)	
LCX	24 (21.8)	12 (30.0)	12 (17.1)	0.150
Proximal LCX ≥ 70%	7 (6.4)	4 (10.0)	3 (4.3)	
RCA	31 (28.2)	12 (30.0)	19 (27.1)	0.830
Proximal RCA ≥ 70%	7 (6.4)	2 (5.0)	5 (7.1)	
Any LM disease or proximal coronary artery disease	22 (20.0)	8 (20.0)	14 (20.0)	1.000
Revascularization				
PCI	11 (10.1)	10 (25.0)	1 (1.4)	<0.001
CABG	19 (17.4)	0 (0.0)	19 (27.5)	<0.001

Data shows is n (%) or mean±SD
*significant CAD defined as left main diameter stenosis ≥ 50% and proximal LAD stenosis ≥ 70%
CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; LAD, left anterior descending; LCX, left circumflex; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement

Table 7. Computed tomography angiography of aorta and calcification pattern in patients undergoing TAVR and SAVR

	TAVR (n=40)	SAVR (n=70)	*p*-value
Aortic valve size	27.3±3.8	27.8±3.2	0.530
Maximum aortic valve annulus diameter, mm	20.9±2.9	21.7±3.0	0.370
Minimum aortic valve annulus diameter, mm	4.4±1.1	3.9±0.5	0.490
Aortic valve annulus area, cm^2	76.8±10.5	78.6±7.0	0.500
Aortic valve annulus perimeter, mm	2,878.4±1,626.7	3,908.7±2,145.2	0.040
Aortic valve calcium score*	2,019.6±1,816.4	2,001.8±2,783.1	0.980
Coronary calcium score**			
Calcium distribution pattern			
Zone i) LVOT	3 (7.5)	10 (14.3)	0.368
Zone ii) aortic annulus to STJ	22 (55.0)	18 (25.7)	0.004*
Zone iii) coronary ostium/ascending aorta	24 (60.0)	21 (30.0)	0.003*
Zone iv) aortic arch	39 (97.5)	58 (82.9)	0.029*
Zone v) descending aorta	40 (100.0)	58 (82.9)	0.004*

Data shows is n (%) or mean±SD, *aortic valve calcium score was assessed in 31 (77.5%) and 32 (45.0%) patients in the TAVR and SAVR, respectively, **coronary calcium score was assessed in 13 (32.5%) and 22 (31.4%) patients in the TAVR and SAVR, respectively.
LVOT, left ventricular outflow tract; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; STJ, sinotubular junction

In the current study, patients with bicuspid aortic valves constituted 32.7% of the overall population, and the majority (81.0%) underwent SAVR. The high proportion of SAVR in bicuspid AS patients can be explained by their age at presentation. Wanchaitanawong et al. reported that patients with bicuspid AS had higher AV calcium scores than those with degenerative AS (17). This could explain why in the present study the mean AV score of patients who underwent SAVR was higher than that of the TAVR group.

We excluded patients who underwent PCI for more than 2 years as we wanted to ensure that the major cause of dyspnea leading to AV intervention was primarily AS rather than concomitant obstructive CAD. Including patients who had already undergone revascularization could reflect that their symptoms were primarily the consequence of AS.

In the present analysis, calcium at the coronary ostium and descending aorta were the predictors of significant CAD. These findings are in line with the report by Kälsch and colleagues (18) that observed a correlation between descending aorta calcification and coronary calcium score. On the contrary, Wong (19) and colleagues reported that calcification in the thoracic aorta was not found to correlate with the coronary calcium score or the presence of coronary heart disease in asymptomatic patients.

The association between the presence of calcification in the descending aorta and significant CAD may be attributable to differences in the tissue composition between the descending and ascending aorta. The wall thickness of the thoracic aorta is generally less than that of the ascending aorta. Furthermore, the ascending aorta contains a higher proportion of collagen and elastin compared to the descending aorta. Additionally, the smooth muscle cells (SMCs) in the ascending aorta originate from the ectoderm, while those in the descending aorta originate from the mesoderm. This is similar to the origin of SMCs in the coronary artery which stem from the proepicardium and are also derived from the mesoderm. It has also been reported that the elastin fiber in the descending aorta has the same compontents as the aortic valve. This elastin plays a role in generating sclerosis leading to AS, calcium deposition in the descending aorta and in CAD (20-23).

In previous studies, AV calcium scores have been reported to be associated with the prevalence and extent of obstructive CAD as assessed by CT coronary angiography (24). However, we did not include the aortic valve calcium score or the coronary artery calcium score in the regression analysis due to missing data on the non-systematic assessment of both scores in the study population.

According to our findings, non-contrast CT of the aorta is associated with significant CAD and therefore could be used as screening tool for patients who are appropriate candidates for invasive coronary angiogram. The implementation of a strategy based on CT of the aorta may enable the avoidance of ICA in a significant subset of patients undergoing aortic valve interventions.

Recent cumulative data has shown that performing PCI either in the same session as or after transcatheter aortic valve implantation is better than performing it before transcatheter aortic valve implantation. Pre-TAVR PCI is associated with risks of contrast-induced nephropathy, bleeding, and stroke. No evidence supports that pre-TAVR PCI provides more clinical benefit than post-TAVR PCI (25, 26). Moreover, PCI after TAVR was associated with improved 2-year clinical outcomes compared with before or index TAVR procedures (27). Thus, there is no requirement to admit the patient for the diagnosis or treatment of CAD before TAVR. Notably, that statement does not align with the current guideline recommendation (6). The findings of the present study can guide physicians when patients with severe AS are in an unstable condition that is not suitable for CT angiography and ICA, but who require emergency TAVR. These findings can shorten the waiting time for the procedure, as the ICA can be done during the TAVR procedure.

This study encountered several limitations. Primarily, the absence of a standardized protocol for conducting CTA of the aorta in all patients scheduled for SAVR led to the exclusion of nearly 50 patients from the SAVR group due to ineligibility based on the inclusion criteria. Addressing and accounting for this limitation should be considered in future research endeavors. In the present analysis, we did not demonstrate a correlation between the degree of calcification and the severity of coronary stenosis as the volumetric analysis of calcium in the aortic wall was not performed. This limitation was due to the lack of a valid method and the requirement for dedicated software for calculating the calcium aortic wall score. Such software is expensive and requires trained physicians to perform the analysis, which means it is often not feasible in real practice since not all centers can acquire such a product. Future multicenter studies with larger numbers of participants dedicated exclusively to TAVR candidates, systematic assessment of AV calcium scores, coronary calcium scores and, calcium distribution patterns would help to confirm the study findings. Additionally, the long-term clinical outcomes and calcium distribution patterns should be further explored.

CONCLUSION

The study identified an association between significant CAD and calcium at the ostial of the coronary and descending aorta as revealed by non-contrast CT of the aorta. The calcification pattern may assist in identifying patients with a heightened likelihood of CAD, especially TAVR candidates. Further studies are needed prior to endorsing the use of CT data in evaluating CAD in patients with moderate to severe AS undergoing aortic valve intervention.

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CONFLICTS OF INTEREST

All the authors declare that they have no conflict of interests.

ADDITIONAL INFORMATION

Authors' contributions

T.T.: provided substantial contributions to the conception or design of the work, performed data collection and statistical analysis, prepared the manuscript and tables; S.D.: performed data collection, statistical analysis and prepared tables; P.S.: interpreted the data and drafted the manuscript; S.K.: critically revised the data and manuscript for important intellectual content and the acquisition, analysis, and interpretation of the data. All authors agreed to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Original Article
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Correlation between the Nutrition Alert Form (NAF) and the Mini Nutritional Assessment Short-Form (MNA-SF) in Hip Fracture Patients

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ABSTRACT

OBJECTIVE Malnutrition in hip fracture patients can lead to poorer outcomes. The Mini Nutritional Assessment Short-Form (MNA-SF) is a reliable tool for identifying malnutrition risk. This study aimed to assess the correlation between the Nutrition Alert Form (NAF) and MNA-SF, using either body mass index (BMI) or calf circumference (CC) scores, in adult inpatients with hip fractures. Additionally, the study sought to correlate NAF scores with other nutrition parameters and comorbidities.

METHODS A cross-sectional study was conducted at Khon Kaen Hospital, involving hip fracture patients. Spearman's rank correlation coefficient (ρ) was utilized for analysis, with the NAF including patient-directed questions and either BMI (NAF-BMI) or total lymphocyte count (NAF-TLC) when BMI data were unavailable.

RESULTS A total of 152 patients were included in the analysis. The mean age was 68.0±16.7 years, with 31.6% being male. Mean body weight and BMI were 55.1±11.9 kg and 22.2±3.8 kg/m², respectively. MNA-SF (BMI) and MNA-SF (CC) identified 44.1% and 79.6% of patients, respectively, as at-risk for malnutrition, while NAF-BMI and NAF-TLC identified 27.6% and 40.1%, respectively. Moderate correlations were observed between NAF-BMI and MNA-SF (BMI) ($\rho = -0.57$, $p < 0.05$) and MNA-SF (CC) ($\rho = -0.58$, $p < 0.05$). NAF-BMI, NAF-TLC and MNA-SF (CC) were also moderately correlated with the Charlson Comorbidity Index.

CONCLUSIONS NAF-BMI and NAF-TLC are both effective screening tools for identifying malnutrition risk in hospitalized hip fracture patients, demonstrating good correlation with MNA-SF as established nutrition screening tools.

KEYWORDS calf circumference, hand grip strength, hip fracture, nutrition alert form, malnutrition, mini nutritional assessment short-form

INTRODUCTION

Hip fractures pose serious public health challenges and can lead to morbidity and mortality. In Thailand, the prevalence of hip fractures is high, ranging from 151.2 to 238.5 per 100,000 and is steadily increasing annually (1). Several factors contribute to the incidence of hip fractures, including bone health, nutritional status, body weight, age, sex, race, and hormonal abnormalities (2). Low body mass and small body size are linked to increased fracture risk, particularly among elderly Caucasian men and women (3).

In elderly patients, malnutrition not only diminishes physical performance and daily living abilities but also heightens the risk of cognitive impairments, surgical complications, prolonged physiotherapy, and mortality (4). Malnutrition is a modifiable risk factor that should be detected early and treated promptly. Screening for nutrition status is recommended for hospitalized adult patients to identify those at risk of malnutrition. Among nutritional screening tools, the Mini-Nutritional Assessment-short form (MNA-SF) outperforms others such as the Malnutrition Universal Screening Tool (MUST) and the Nutritional Risk Score 2002 (NRS-2002) in predicting various functional outcomes including postoperative acute phase following hip fractures and mortality (5). Approximately 52.6% of hip fracture patients are at-risk for malnutrition, as assessed by MNA-SF (6). Although MNA-SF is primarily used for screening malnutrition in the elderly (7), it can also effectively screen hospitalized young and middle-aged adults, predicting in-hospital mortality (8, 9). In this study, we used the MNA-SF, a well-validated tool designed to screen nutritional status in hip fracture patients, to ensure a standardized approach.

Anthropometric indices, including body mass index (BMI), body weight, and serum albumin, are also used to assess nutrition status. Lower scores on these indices are associated with higher rates of complications and poorer functional recovery (10). However, serum albumin levels are not routinely measured for hip fracture patients upon admission. In Thailand, the Society of Parenteral and Enteral Nutrition of Thailand (SPENT) has endorsed the use of the Nutrition Alert Form (NAF) as a nutrition assessment tool for evaluating the nutrition status of hospitalized patients. NAF exhibits high sensitivity and validity across various clinical settings, can be used by non-nutrition experts, and can be interpreted without knowledge of body weight (11). This study attempted to use NAF as a one-step approach for screening and assessing the nutritional status of hospitalized patients with hip fractures. Validated screening tools are essential for early identification of malnutrition risk, enabling prompt nutritional assessment and intervention, resulting in better cost-effectiveness and improved outcomes (10). The primary objective of this study is to investigate the correlation between MNA-SF and NAF in hospitalized patients with hip fractures. Additionally, we aim to assess the prevalence of at-risk malnutrition and evaluate the correlation between nutrition screening tools, anthropometric parameters (BMI, handgrip strength (HGS), calf circumference (CC), and mid-arm circumference (MAC)), laboratory results (creatinine and total lymphocyte count), and comorbidities using the Charlson Comorbidity Index (CCI) in hospitalized hip fracture patients.

METHODS

Population selection and study design

The present study was a cross-sectional study. All hospitalized individuals with hip fractures were selected through simple random sampling at Khon Kaen Hospital's orthopedic ward between August 2022 and December 2023. The sample size required for correlations, a power of 90.0% and a type 1 error rate (α) of 0.05, allowing for a loss of 10.0%, was 144 subjects (12).

We included 165 patients with hip fractures who met the specified criteria, of whom 13 were excluded, resulting in a final analysis of 152 patients. Inclusion criteria were patients aged 18 years or older, diagnosed with hip fractures based on clinical and radiological findings, capable of answering questions and undergoing testing with anthropometric measurements, and willing to participate in the study. Exclusion criteria were patients with multiple fractures, uncontrolled diabetes (HbA1c ≥ 9.0%), active opportunistic infections (in, e.g., AIDS), end-stage renal disease, congestive heart failure, hormonal deficiencies, hemodynamic instability, malignancies, and pregnancy. The study received approval from the Khon Kaen Hospital Institute Review Board in Human Research, Thailand (approval code KEXP65033), and was conducted in accordance with the Helsinki Declaration of 1975. Prior to participation, all participants provided written informed consent.

We gathered demographic information, including age, sex, current medication use, and medical comorbidities, which were assessed using the CCI. Hip fractures were categorized by anatomic region as either intracapsular or extracapsular fractures (13). Additionally, we reviewed the causes of hip fractures and the types of management employed. The American Society of Anesthesiologists (ASA) physical status classification system was used to categorize patients' physiological status into six types perioperatively, aiding in predicting operative risk (14). Pre-fracture functional status was classified as partially dependent, fully independent, or fully dependent.

All participants underwent nutrition screening using tools such as MNA-SF and NAF on the first day of admission. Anthropometric measurements, including body weight (kg), height (cm), MAC (cm), CC (cm), and HGS (kg), were taken. BMI was calculated using the formula BMI = weight (kg) ÷ height (m^2). Preoperative blood parameters, including BUN (mg/dL), creatinine (mg/dL), and total lymphocyte count (TLC: cells/mm^3), were recorded for analysis.

Anthropometric measurements

Body weight and height

As all patients had hip fractures, a digital weighing scale was used to measure body weight with the patient in a stretcher or wheelchair, and actual body weight was determined by subtracting the weight of the stretcher or wheelchair on the first day of admission. Previous body weight was assessed through history-taking to calculate weight loss. Height was estimated using the half-arm span, from the middle of the sternal notch to the tip of the middle finger, and calculated by doubling the half-arm span (6).

Mid arm circumference (MAC)

MAC was measured in centimeters using a non-stretchable plastic tape. The measurement was taken at the midpoint between the olecranon process and the acromion of the dominant arm while patients were in the supine position, as pain limited their ability to sit (15).

Calf circumference (CC)

CC was measured using a measuring tape at the largest circumference of the calf of the non-fractured leg, with the patient in a supine position and the knee bent at a 90-degree angle. In the MNA-CC, the cutoff point for CC was 31 cm for both genders (16).

Handgrip strength (HGS)

HGS was measured three times using handgrip dynamometry while patients were in the supine position, as pain limited their ability to sit. The highest value obtained using the dominant hand was used in the analysis (15).

Nutrition screening tools

Nutrition Alert From (NAF)

The Society of Parenteral and Enteral Nutrition of Thailand recommends the NAF for assessing the nutritional status of hospitalized patients. Due to its high sensitivity, NAF can be used as a screening tool to stratify nutritional status even by non-nutrition experts. The NAF consists of patient-oriented questions that evaluate weight changes, the quality and quantity of food consumed, gastrointestinal symptoms, the patient's food accessibility, comorbidities, and basic anthropometric measurements like body weight and height, collectively referred to as NAF-BMI. Unlike many tools that rely solely on weight and height, NAF-TLC can be used as an alternative measure when a patient's body weight is unknown. The cutoff scores for NAF are as follows: an A score between 0 and 5 indicates no risk of malnutrition, a B score between 6 and 10 indicates a moderate risk of malnutrition, and a C score greater than 11 indicates a severe risk of malnutrition (11).

Mini Nutritional Assessment Short-Form (MNA-SF)

The MNA-SF is a validated nutrition screening tool used not only in the elderly but also in hospitalized young and middle-aged adults which is capable of predicting outcomes (8, 9). The tool comprises six questions, including assessments of decline in food intake, weight loss over the past three months, mobility, psychological stress or acute disease, neuropsychiatric problems, and BMI or CC when BMI assessment is not possible, indicated by MNA-SF (BMI) and MNA-SF (CC), respectively. The cutoff point for CC related to the risk of malnutrition is 31 cm for both sexes (16). With scores ranging from 0 to 14, the cutoff points are used to classify the risk of malnutrition: scores of 0-7 indicate malnutrition, 8-11 indicate being at risk of malnutrition, and 12-14 indicate a normal nutritional status.

Statistical analysis

All analyses were conducted using IBM SPSS version 16. The normality of the data was assessed using the Shapiro-Wilk test. Quantitative variables are presented as the mean ± standard deviation (SD) or as medians with interquartile ranges (IQR), depending on the normality of the data. Categorical variables are expressed as numbers or percentages and were analyzed using the chi-square test, or Fisher's exact test where appropriate. Continuous variables were categorized based on their cut-off values for malnutrition.

The Spearman rank correlation coefficient (ρ) was used to evaluate the correlation among NAF, MNA-SF, anthropometric parameters, CCI, and laboratory results. The strength of the association was determined based on the absolute value of the Spearman rank correlation coefficients, with ranges of 0.00-0.29, 0.30-0.49, 0.50-0.69, 0.70-0.89, and 0.90-1.00 indicating negligible, low, moderate, high, and very high correlation, respectively (17). MNA-SF is primarily used for screening malnutrition in the elderly (7), but it can also effectively screen hospitalized young and middle-aged adults. Therefore, the subgroup analysis of the correlation between MNA-SF (BMI) and NAF-BMI included individuals aged at least 65 years old (elderly) and adults aged less than 65 years old. Cohen's kappa coefficient was employed to assess the agreement between NAF-BMI and the other screening tools. Statistical significance was considered at a $p < 0.05$, and all tests were two-sided.

RESULTS

Demographics and clinical characteristics

A total of 152 patients who met the inclusion criteria were enrolled for analysis. The participants had a mean age of 68.0±16.7 years, with 31.6% being male. The mean body weight was 55.1± 11.9 kg, and the mean BMI was 22.2±3.8 kg/m^2.

The causes of hip fractures were falling in 77.0% of cases, traffic accidents in 21.1% of cases, and pathological fractures in 1.9% of cases. The diagnosis of hip fractures, confirmed by x-ray imaging, showed that 46.1% were intracapsular fractures and 53.9% were extracapsular fractures. Around 92.1% of patients with hip fractures underwent surgery, while 7.9% were placed on skin traction.

Regarding pre-fracture functional status, 80.2% were fully independent, 0.7% were partially dependent, and 19.1% were either fully dependent or bedridden. The median CCI was 3 (IQR 1.25-4). In terms of the ASA physical classification, 34.2% were classified as healthy, 64.5% as having mild systemic disease, and 1.3% as having severe systemic disease.

For anthropometric assessments, the mean CC for male participants was 31.1±4.8 cm, and for female participants, it was 29.0±3.5 cm. The mean MAC for male participants was 25.8±3.8 cm, and for female participants, it was 24.1±3.3 cm. The mean HGS was 26.0±12.4 kg for male participants and 14.0±9.4 kg for female participants. Anthropometric indices, including CC, MAC, and HGS, differed significantly among different nutritional status groups, with lower levels observed in the malnutrition group at admission.

Upon admission, the median total lymphocyte count was 1,298.84 cells/uL (IQR 919.35-1,752.20). The mean blood urea nitrogen (BUN) level was 17.7 ± 11.1 mg/dL, and the median creatinine level was 0.81 mg/dL (IQR 0.66-1.08). There were no significant differences among the different nutritional statuses. Baseline characteristics categorized by nutritional status are summarized in Table 1.

Prevalence of at-risk malnutrition

The prevalence of at-risk malnutrition/malnutrition, assessed using NAF-BMI and NAF-TLC based on the standard cut-off values of NAF, was 27.6% and 40.1%, respectively. Meanwhile, MNA-SF (BMI) and MNA-SF (CC) showed rates of 44.1% and 79.6%, respectively. The number and percentage of hip fracture patients with at-risk malnutrition are summarized in Tables 2 and 3, classified by MNA-SF (CC), MNA-SF (BMI), NAF-BMI, and NAF-TLC.

Correlation between NAF, MNA-SF (BMI), MNA-SF (CC), Charlson comorbidity index (CCI), anthropometric parameters and laboratory results

The NAF-BMI score has a very high and significant correlation with NAF-TLC, with $\rho = 0.91$, $p < 0.05$. The NAF-BMI score showed a significant inverse correlation with MNA-SF (BMI) and MNA-SF (CC), with moderate correlations of $\rho = -0.57$, $p < 0.05$ and $\rho = -0.58$, $p < 0.05$, respectively. The correlation coefficients for NAF-BMI with other outcomes were as follows: CCI, $\rho = 0.64$, $p < 0.05$; MAC, $\rho = -0.29$, $p < 0.05$; HGS, $\rho = -0.38$, $p < 0.05$; CC, $\rho = -0.34$, $p < 0.05$; and BMI, $\rho = -0.22$, $p < 0.05$. The other correlations are shown in Table 4 and Supplementary Figure 1.

Table 1. Baseline characteristics of the study population stratified by MNA-SF (BMI) categories.

Parameters	Overall N=152	MNA-SF (≥ 12) N=85 (55.9%)	MNA-SF (8-11) N=63 (41.5%)	MNA-SF (0-7) N=4 (2.6%)	*p*-value†
Age (years)	68.0±16.7	62.3±18.3	74.9±10.9	81.7±6.1	<0.05
Female (%)	104 (68.4)	51 (60.0)	50 (79.4)	3 (75.0)	<0.05
Body weight (kg)	55.1±11.9	61.5±10.4	47.3±8.4	44.3±5.6	<0.05
Body mass index (kg/m^2)	22.2±3.8	24.1±3.1	19.8±3.1	18.8±2.4	<0.05
Calf circumference (cm)					
Male	31.1±4.8	32.8±4.3	27.3±3.5	25.1*	<0.05
Female	29.0±3.5	30.4±3.6	27.8±3.0	25.9±0.7	<0.05
Mid arm circumference (cm)					
Male	25.8±3.8	27.1±3.4	22.6±2.7	22.1*	<0.05
Female	24.1±3.3	25.7±3.2	22.6±2.6	23.2±4.0	<0.05
Hand grip strength (kg)					
Male	26.0±12.4	29.2±12.3	17.7±8.6	23.2*	<0.05
Female	14.0±9.4	14.8±7.6	12.1±4.7	9.4±5.4	0.053
Total lymphocyte count (cells/uL)‡	1,298.8 (919.35, 1752.2)	1,315.8 (928, 1,801.8)	1,276.9 (918.2, 1,593.9)	1371.6 (692.5, 2,190.7)	0.75
BUN (mg/dL)	17.7±11.1	16.6±10.2	18.3±11.0	31.5±20.6	0.09
Creatinine (mg/dL)‡	0.81 (0.66,1.08)	0.84 (0.68,1.08)	0.79 (0.64,1.00)	1.57 (1.04,2.34)	0.19
Charlson Comorbidity Index‡	3.0 (1.25,4.0)	3.0 (1.0,4.0)	4.0 (3.0,4.0)	5.0 (4.5,5.5)	<0.05
Functional status (%)					
Fully independent	122 (80.2)	71 (83.5)	50 (79.4)	1 (25.0)	<0.05
Partial dependent	1 (0.7)	1 (1.2)	0 (0.0)	0 (0.0)	
Fully dependent	29 (19.1)	13 (15.3)	13 (20.6)	3 (75.0)	
ASA physical classification (%)					
Normal healthy	52 (34.2)	34 (40.0)	17 (27.0)	1 (25.0)	0.19
Mild systemic disease	98 (64.5)	51 (60.0)	44 (69.8)	3 (75.0)	
Severe systemic disease	2 (1.3)	0 (0.0)	2 (3.2)	0 (0.0)	
Threat to life	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Not expect to survive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Cause of hip fracture (%)					
Falling	117 (77.0)	56 (65.9)	57 (90.5)	4 (100.0)	<0.05
Traffic accident	32 (21.1)	27 (31.8)	5 (7.9)	0 (0.0)	
Pathological fracture	3 (1.9)	2 (2.4)	1 (1.6)	0 (0.0)	
Type of hip fracture					
Intracapsular fracture	70 (46.1)	41 (48.2)	27 (42.9)	2 (50.0)	0.37
Extracapsular fracture	82 (53.9)	44 (51.8)	36 (57.1)	2 (50.0)	
Management of hip fracture (%)					
Skin traction	12 (7.9)	8(9.4)	4 (6.3)	0 (0.0)	0.68
Surgery	140 (92.1)	77 (90.6)	59 (93.7)	4 (100.0)	

*Data number = 1
Data are presented as mean ± standard deviation or number (%); ‡median (interquartile range).
†Kruskal-Wallis rank sum test; Fisher's exact test, significant data $p < 0.05$

MNA-SF (BMI) also showed moderate correlations with anthropometric indices including MAC, CC, and BMI, while MNA-SF (CC) had a moderately inverse correlation with CCI. However, NAF-BMI, NAF-TLC, MNA-SF (BMI), and MNA-SF (CC) only showed a negligible correlation with the laboratory results in the present study. The correlations between each nutrition screening tool and other parameters are summarized in Table 4. The agreement evaluated by Cohen's kappa between NAF-BMI and the other tools, including NAF-TLC, MNA-SF (BMI), and MNA-SF (CC), was as follows: 0.60 (95% CI 0.48 to 0.73, $p < 0.05$), 0.41 (95% CI 0.27 to 0.54, $p < 0.05$), and 0.17 (95% CI 0.10 to 0.25), respectively.

A scatter plot illustrating the correlation between NAF-BMI and MNA-SF (BMI) in two age subgroups, at least 65 years and under 65 years, is shown in Figure 1 and Supplement Figure 2. The correlation of NAF-BMI and MNA-SF (BMI) in the

Table 2. Risk of malnutrition among the study population stratified by MNA-SF (BMI) categories.

A Screening Tool	Total (%) (n=152)	MNA-SF (≥ 12) (n=85)	MNA-SF (8-11) (n=63)	MNA-SF (0-7) (n=4)	*p*-value*
NAF-BMI score (%)					< 0.05
A (0-5)	110 (72.4)	77 (90.6)	33 (52.4)	0 (0.0)	
B (6-10)	36 (23.7)	8 (9.4)	27 (42.9)	1 (25.0)	
C (≥11)	6 (3.9)	0 (0.0)	3 (4.8)	3 (75.0)	
NAF-TLC score (%)					< 0.05
A (0-5)	91 (59.9)	66 (77.6)	25 (39.7)	0 (0.0)	
B (6-10)	53 (34.9)	18 (21.2)	34 (54)	1 (25.0)	
C (≥11)	8 (5.2)	1 (1.2)	4 (6.3)	3 (65.0)	

Data are presented as number (%); *Fisher's exact test, significant data $p < 0.05$
BMI, body mass index; MNA-SF, Mini Nutritional Assessment Short-Form; NAF, Nutrition Alert Form; TLC, total lymphocyte count

Table 3. Risk of malnutrition among the study population stratified by MNA-SF (CC) categories.

A Screening Tool	Total (%) (n=152)	MNA-SF (≥ 12) (n=31)	MNA-SF (8-11) (n=111)	MNA-SF (0-7) (n=10)	*p*-value*
NAF-BMI score (%)					< 0.05
A (0-5)	110 (72.4)	31 (100.0)	77 (69.4)	2 (20.0)	
B (6-10)	36 (23.7)	0 (0.0)	32 (28.8)	4 (40.0)	
C (≥11)	6 (3.9)	0(0.0)	2 (1.8)	4 (40.0)	
NAF-TLC score (%)					< 0.05
A (0-5)	91 (59.9)	29 (93.5)	61 (55.0)	1 (10.0)	
B (6-10)	53 (34.9)	2 (6.5)	47 (42.3)	4 (40.0)	
C (≥11)	8 (5.2)	0 (0.0)	3 (2.7)	5 (50.0)	

Data are presented as number (%); *Fisher's exact test, significant data $p < 0.05$
BMI, body mass index; MNA-SF, Mini Nutritional Assessment Short-Form; NAF, Nutrition Alert Form; TLC, total lymphocyte count

Table 4. Correlation between NAF-BMI, NAF-TLC, MNA-SF (BMI), MNA-SF (CC), Charlson Comorbidity Index (CCI), and anthropometric parameters.

Parameters	NAF-BMI score		NAF-TLC score		MNA-SF (BMI)		MNA-SF (CC)	
	ρ†	*p*-value	ρ†	*p*-value	ρ†	*p*-value	ρ†	*p*-value*
NAF-BMI			0.91	<0.05	-0.57	<0.05	-0.58	<0.05
CCI	0.64	<0.05	0.66	<0.05	-0.36	<0.05	-0.50	<0.05
MAC (cm)	-0.29	<0.05	-0.21	<0.05	0.62	<0.05	0.30	<0.05
HGS (kg)	-0.38	<0.05	-0.36	<0.05	0.38	<0.05	0.47	<0.05
CC (cm)	-0.34	<0.05	-0.28	<0.05	0.57	<0.05	0.49	<0.05
BMI (kg/m^2)	-0.22	<0.05	-0.15	>0.05	0.66	<0.05	0.13	>0.05
TLC (cells/mm^2)	-0.09	>0.05	-0.43	<0.05	0.05	>0.05	0.06	>0.05
BUN (mg/dL)	0.17	<0.05	0.18	<0.05	-0.12	>0.05	-0.22	<0.05
Creatinine (mg/dL)	0.19	<0.05	0.20	<0.05	0.05	>0.05	-0.12	>0.05

†Spearman's Rank Order Correlation (ρ), correlation is significant at the 0.05 level (2-tailed).
BMI, body mass index; BUN, blood urea nitrogen; CC, calf circumference; HGS, hand grip strength; MAC, mid-arm circumference; MNA-SF, Mini Nutritional Assessment Short-Form; NAF, Nutrition Alert Form; TLC, total lymphocyte count

age group ≥ 65 years old showed a moderate correlation of $\rho = -0.55$, $p < 0.05$, while the correlation was low in the age group < 65 years old, with $\rho = -0.40$, $p < 0.05$ (Supplementary Table 1).

DISCUSSION

In this study, we found a moderate correlation between NAF-BMI and MNA-SF (BMI) in hospitalized hip fracture patients. The prevalence of

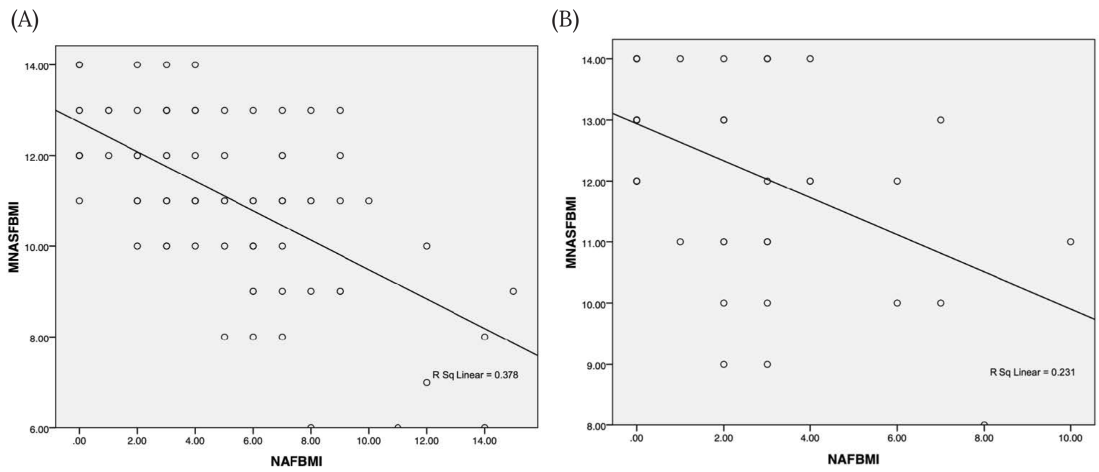

Figure 1. Scatter plot illustrating the correlation between NAF-BMI and MNA-SF (BMI) in (A) participants aged ≥ 65 years and (B) participants aged < 65 years

at-risk malnutrition and malnutrition, as determined by NAF-BMI and NAF-TLC, was 27.6% and 40.1%, respectively, while MNA-SF (BMI) and MNA-SF (CC) showed rates of 44.1% and 79.6%, respectively. This study is the first to assess the correlation between NAF and MNA-SF in hospitalized patients with hip fracture using both simple and validated nutrition screening tools.

Insufficient energy and protein intake are prevalent both before admission as preexisting malnutrition and after hip surgery, exacerbated by the catabolic response to injury and surgery (18). Consequently, malnutrition and sarcopenia can hinder rehabilitation, prolong hospital stays, and worsen clinical outcomes (6). Overall, malnutrition in hip fracture patients can lead to increased morbidity, mortality, and healthcare costs (19). The prevalence of malnutrition ranges from 4% to 39.4% according to various nutritional assessment tools (20), with half of hip fracture patients at risk of malnutrition as assessed by MNA-SF (18). While the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends postoperative oral nutritional supplementation (ONS) for geriatric hip fracture patients without determining their nutritional status, hospitalized patients with preexisting malnutrition have been shown to benefit from ONS, which has also been proven to be cost-effective (21). Despite SPENT recommending NAF as an assessment tool, NAF can also be utilized as a one-step approach to screen for and assess malnutrition risk due to its high sensitivity, around 80.0-97.0% and high specificity, around 75.0-91.3% (22-24), and validity in various clinical settings to evaluate the nutrition status of hospitalized patients within 48 hours of admission. In hospitals with limited resources, NAF can be used to prioritize patients at preexisting risk of malnutrition and identify malnourished patients in one step, allowing for urgent nutrition interventions. This approach can also likely lead to time saving.

A previous study found that the NAF-BMI exhibited a moderate agreement with the full form of the MNA, with Cohen's kappa coefficient of 0.56 (22). As a one-step approach for screening and assessing nutrition status, our study also demonstrated a moderate correlation and a moderate agreement between NAF-BMI and MNA-SF (BMI). There is also a moderate correlation and slight agreement between NAF-BMI and MNA-SF (CC). A previous study validated both forms of MNA-SF (BMI) and MNA-SF (CC) for assessing the nutritional status of older adults. However, the sensitivity of MNA-SF (BMI) and MNA-SF (CC) was 72.0% and 92.0%, respectively, while the specificity was 95.6% and 73.8%, respectively. Thus, the prevalence of malnutrition assessed by MNA-SF (BMI) was 16.5% in free-living elderly, similar to the MNA full form, whereas MNA-SF (CC) overestimated the prevalence at 38.0% (25). Similarly, our study identified 44.1% and 79.6% of patients as at risk for malnutrition and malnourishment, respectively, using MNA-SF (BMI) and MNA-SF (CC). Furthermore, our study recommended using MNA-SF (BMI) as the screening tool due to the risk misclassification of MNA-SF (CC) (26). The cut-off point for CC is population-specific and depends on factors such as sex, age, BMI, and country. It should be validated against a reliable tool, such as the skeletal muscle mass index. For the elderly Asian population, the cut-off ranges from 23.6 to 34.0 cm in men and 23.6 to 33.0 cm in women (27, 28). Furthermore, there are still scant studies examining a cut-off value for young and healthy adult populations (29). Therefore, the overdiagnosis of at-risk malnutrition using the MNA-SF (CC) may be due to the high cut-off value of CC in the test. However, another study with a larger sample size showed a similar prevalence of at-risk malnutrition/malnutrition, evaluated by MNA-SF (BMI) and MNA-SF (CC), at 27.4% and 27.7% in free-living elderly, respectively (30). Despite the MNA-SF being a validated nutritional screening tool for both elderly and middle-aged adults (8, 9), our study highlighted a stronger correlation between NAF and MNA-SF in the elderly group. Therefore, both MNA-SFs can be considered rapid, easy, and reliable tools for identifying the risk of malnutrition, especially in the elderly.

In our study, we observed a higher CCI among hip fracture patients classified as at-risk malnourished and malnourished when compared to those with normal nutrition status as classified by the MNA-SF. The CCI score is commonly employed to predict mortality in hip fracture patients (31). There exists a moderate correlation between CCI and MNA-SF (CC). Among patients with hip fractures, the ASA class and a high CCI score, particularly ≥ 4, can predict short-term and long-term mortality (32, 33). Previous studies have also shown that patients identified as being at risk of malnutrition or malnourished according to the MNA-SF tend to have a higher CCI (34). Certain comorbidities incorporated into the CCI, such as chronic obstructive pulmonary disease and chronic kidney disease, are known to be linked with systemic inflammation. This association often leads to heightened metabolic demands and anorexia, which in turn can culminate in the development of sarcopenia and malnutrition. These underlying mechanisms may elucidate the elevated risk of malnutrition observed in hip fracture patients with higher CCI scores. Consistent with our findings, previous research has demonstrated an inverse association between MNA-SF and HGS with CCI score (34). While nutrition status may be confounded by higher comorbidities, the combination of malnutrition and a high CCI may lead to additional poorer outcomes. The compounded impact of malnutrition and diminished HGS has been shown to escalate the risk of all-cause mortality (35).

Several noninvasive anthropometric indices, such as CC and MAC, reflect muscle mass and nutritional status, while HGS serves as an indicator of low muscle strength and is a component of sarcopenia diagnosis. These indices are particularly relevant for assessing the prognosis and functional outcomes of hip fractures, especially in the elderly (15, 16, 36). In adults under 60 years old with hip fractures, low levels of physical activity have been shown to be associated with low HGS and higher ASA grade, potentially leading to higher mortality rates (37). MAC is used to represent muscle mass and subcutaneous fat, especially when the edematous state commonly affects CC. Both MAC and CC demonstrate similar diagnostic performance in diagnosing sarcopenia (15). Our study also revealed a significant correlation between anthropometric indices, including HGS, CC, and MAC, and nutrition status as assessed by both NAF and MNA-SF, consistent with previous studies which have shown varying degrees of correlation (38). However, the measurement technique for hand grip strength and the cutoff value in patients with hip fractures are limited by the supine position.

In a systematic review and meta-analysis, low serum albumin levels, malnutrition, and low TLC were identified as predictors of poorer outcomes following hip fracture surgery (39). Currently, serum visceral proteins such as albumin and prealbumin are utilized to forecast surgical outcomes and mortality rates (40). However, there is no single laboratory marker that comprehensively represents nutritional status. Our study did not observe a significant correlation between laboratory results and nutrition status.

This study represents a pioneering effort in assessing the prevalence of at-risk malnutrition and malnutrition among patients with hip fractures through the utilization of the NAF. Additionally, it undertakes a comparative analysis of NAF with various screening tools, including the MNA-SF, anthropometric indices, and laboratory markers, within the context of hospitalized hip fracture patients. Furthermore, this study seeks to extend the application of the MNA-SF to screen for malnutrition in young adults, a demographic for which scant studies have employed the MNA-SF for this purpose (8, 9).

The present study is subject to several limitations that warrant acknowledgment. Firstly, its cross-sectional design precludes the establishment of a temporal relationship between nutrition status and clinical outcomes. Secondly, there remains uncertainty regarding the efficacy of nutrition screenings for detecting malnutrition and administering early nutrition interventions compared to providing oral nutrition supplements to all patients undergoing hip fracture surgery, as recommended by current guidelines. Lastly, we observed variability in malnutrition prevalence when altering certain factors within the same screening tools, despite significant correlations among these tools. Future studies should prioritize investigating outcomes and cost-effectiveness following nutrition interventions among either hip fracture patients with pre-existing malnutrition or without malnutrition.

CONCLUSIONS

Our findings suggest that NAF is an effective screening tool for identifying malnutrition risk in hip fracture patients, correlating well with MNA-SF as established nutrition screening tools. NAF-TLC and MNA-SF (CC) can serve as simple tools to screen for malnutrition risk in hospitalized hip fracture patients, especially when BMI cannot be accessed. The varying prevalence rates of at-risk malnutrition need further evaluation, and prompt nutrition intervention in those malnourished cases should be assessed in further studies.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION:

C.U., T.P.: conceptualization, methodology, software, writing – review & editing; C.U., N.J.: data curation, writing-original draft preparation; T.P.: visualization, investigation; K.S, K.C.: supervision; N.J.: software, validation

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

Supplementary materials

The following supporting information can be downloaded at: Supplementary appendix

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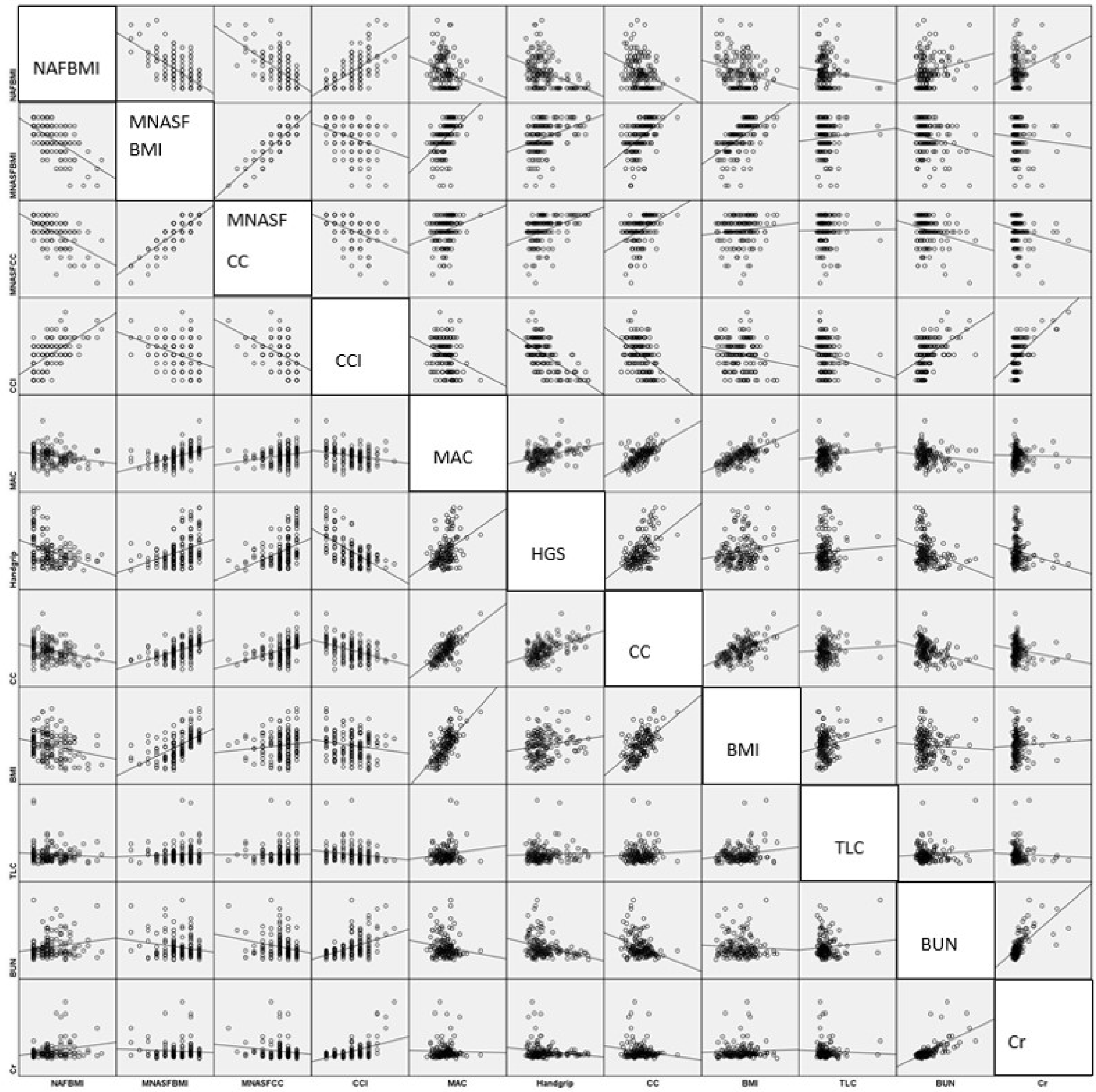
Supplementary Figure 1: Correlation between NAF-BMI, MNA-SF (BMI), MNA-SF (CC), Charlson Comorbidity Index, anthropometric parameters, and laboratory results.



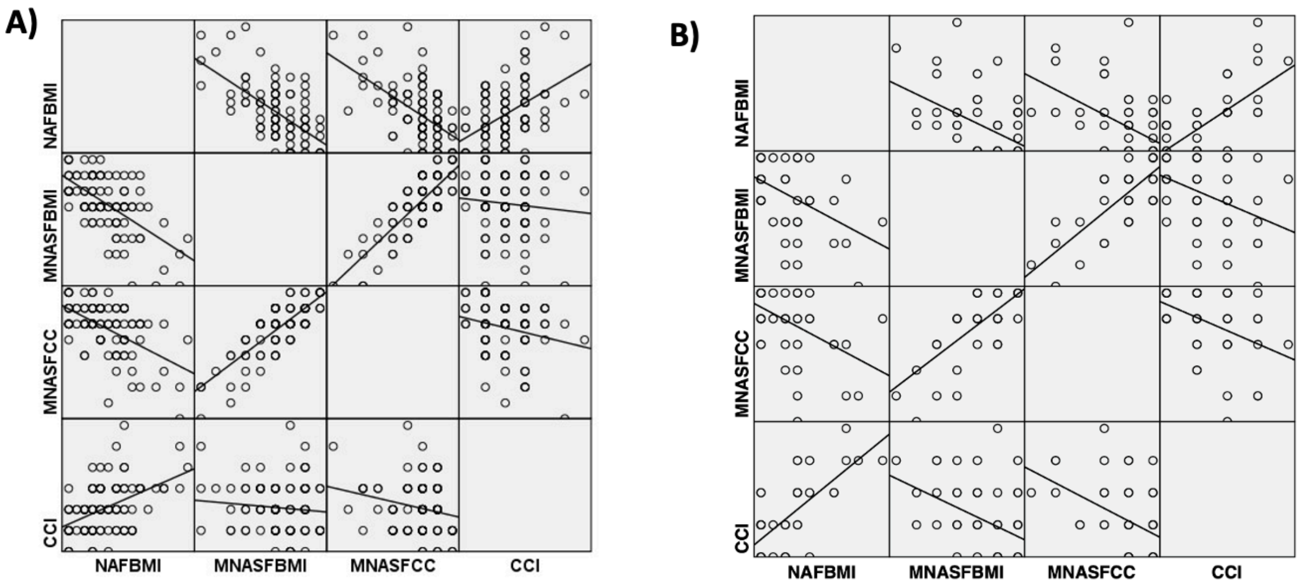
Supplement Table 1: Correlation between NAF, MNA-SF (BMI), MNA-SF (CC), Charlson comorbidity index (CCI) in age group ≥65 years, < 65 years

Parameters	NAF-BMI score		MNA-SF (BMI)		MNA-SF (CC)	
Age group	ρ †	*p*-value	ρ †	*p*-value	ρ †	*p*-value
NAF-BMI score in age group ≥65 years			-0.55**	< 0.05	-0.48**	< 0.05
NAF-BMI score in age group <65 years			-0.40**	< 0.05	-0.47**	< 0.05
CCI in age group ≥65 years	0.47**	< 0.05	-0.08	0.47	-0.177	0.08
CCI in age group <65 years	0.61**	< 0.05	-0.42**	< 0.05	-0.41**	< 0.05

†Spearman's Rank Order Correlation(ρ)

**Correlation is significant at the 0.01 level (2-tailed).

Supplement Figure 2: Scatter plot showed the correlation NAF-BMI, MNA-SF and CCI A) age group ≥65 years B) age group < 65 years.



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Original Article

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Predicting Hospital Admission of Patients at Triage in the Emergency Department at Lampang Hospital

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ABSTRACT

OBJECTIVE This study aims to develop a model that can help predict the likelihood of hospital admission for patients at the triage point in Lampang Hospital's Emergency Department.

METHODS The study was designed around Clinical Prediction Rules and was conducted as a retrospective cohort study using data from July 2021 to January 2022 input through the Smart ER program. Patients were categorized into two groups: admit and discharge. Statistical analysis involved both univariable and multivariable logistic regression analyses, presenting discrimination values with area under the receiver operating characteristic (AUROC), testing precision with a calibration plot, analyzing internal validation using the Bootstrapping method, and creating a risk curve to find the balanced cutoff point. The study then divided the predictions into one of three groups: Admit, Consult, and Discharge. Decision curve analysis (DCA) was performed and an application was developed and integrated into the Smart ER program for real-time analysis.

RESULTS Out of 37,474 patients screened, 18,056 were excluded leaving 19,418 patients eligible for complete case analysis. Predictors of hospital admission included age, emergency level, vital signs, mode of hospital arrival, and prominent symptoms according to criteria-based dispatch (CBD) (criteria-based dispatch). The Admission Model showed an AUROC of 0.8934 (95% CI, 0.8890-0.8980); the calibration plot demonstrated that predicted values closely matched actual observed values; internal validation using the Bootstrapping method yielded a C-statistic of 0.8920 (95% CI, 0.888-0.895); and the balanced risk curve indicated over admission at 3.8% and over discharge at 3.7%.

CONCLUSIONS The Admission Model provides high AUROC and precision values. The model's three-group division is likely to be beneficial in practical application.

KEYWORDS patient admission, clinical decision rules, models, statistical, overcrowding

INTRODUCTION

The Emergency Department (ED) at Lampang Hospital serves patients both during and outside normal working hours, handling an average of 200-250 patients per day. Each patient undergoes triage according to the Ministry of Public Health (MOPH) ED Triage principles (1) which classify emergency levels from 1 to 5. Level 1 indicates critical conditions requiring immediate intervention to prevent death, while level 5 indicates non-urgent conditions. Triage is conducted at the professional nursing station where patients' chief complaints are recorded, vital signs measured, pain scales assessed, and patient type (trauma or non-trauma) classified. Currently, ED Lampang Hospital has implemented an Electronic Health Record system, utilizing the 'Smart ER' program to digitally store data which allows for real-time emergency medical registry analysis.

Overcrowding is a frequent issue in the ED (2-6), often exacerbated by physicians' indecisiveness regarding whether patients should be admitted or discharged (2, 3), particularly among less experienced physicians. This indecision often leads to unnecessary laboratory tests, causing delays for patients who could potentially be admitted immediately. At the ED of Lampang Hospital, this can result in delays of at least 2-3 hours in the ED.

Previous studies have highlighted the importance of several parameters in predicting hospital admissions, with a focus on vital signs such as temperature, pulse rate, blood pressure, respiration rate, and blood oxygen saturation level. Other important factors to consider include age, sex, triage levels, mode of transportation, and Glasgow Coma scale (GCS) score (7).

The 'Smart ER' program stores large amounts of data which can be analyzed using big data analytics to predict the chances of hospital admission. This tool can help guide newly graduated doctors in making more efficient admission decisions (8, 9), potentially alleviating ER overcrowding both now and in the future.

The objective of this study is to predict the likelihood of hospital admission at the triage point in Lampang Hospital's ED utilizing electronic data from the 'Smart ER' program.

METHODS

This prognostic prediction research employed a retrospective cohort design to assess the likelihood of hospital admission at the triage point in the ED of Lampang Hospital. The study setting was the triage area of the ED, where patients are initially assessed before receiving further medical services. Data were collected from the 'Smart ER' electronic program which is used for managing patient information and triage processes.

Data were retrospectively collected for all patients screened before receiving emergency room services at Lampang Hospital from July 1, 2022 to January 31, 2023 and included patients who were triaged at Lampang Hospital's ED between July 1, 2022 and January 31, 2023. Inclusion criteria consisted of all patients who underwent triage during this period and who were recorded in the 'Smart ER' system. Exclusion criteria included patients who were on intubation before triage, refused treatment, were transferred to the outpatient department, died before receiving ED services or at the ED, left without being seen by medical staff, or had incomplete data in the hospital record system.

This study utilized a range of determinants (independent variables) derived from real-time electronic data captured through the 'Smart ER' program at Lampang Hospital. Variables included gender, age, presenting symptoms (criteria based dispatch, CBD), triage level, time of hospital arrival, referral source, vital signs (blood pressure, pulse rate, respiratory rate, temperature, GCS), pain scale, patient type (trauma, non-trauma), and shift timings. The primary outcome variable was the likelihood of hospital admission

Data were extracted from the 'Smart ER' program and exported to Excel for preliminary cleaning. Statistical analysis was conducted using STATA® version 18. The study used a "complete case analysis" approach, avoiding data imputation. Patient characteristics were compared using exact probability tests for categorical variables and the Student's t-test or Wilcoxon rank sum test for continuous variables. Multivariable logistic regression was employed to analyze predictors of hospital admission, with the model's discrimination ability assessed using the area under the receiver operating characteristic (AUROC) curve. Model validity was tested using calibration plots and internal validation through bootstrapping. Decision curve analysis and a risk curve were also utilized to enhance the clinical applicability of the predictive model.

The sample size was calculated using Dr. Richard D. Riley's method (10) as suggested in modern clinical epidemiology, considering a C-statistic of 0.8, 20 parameters, an admission prevalence of 41.42%, and a shrinkage factor of 0.99, resulting in a minimum required sample size of 6,738. To account for potential missing data, a 30% buffer increased the total required sample size to approximately 10,000 cases.

Ethical considerations

The study maintained strict patient confidentiality by anonymizing personal identifiers such as name, hospital ID, and national ID number. Ethics approval was secured from the Lampang Hospital Ethical Research Committee (approval No. 074/66).

Definition

The CBD (11) for sorting and prioritizing emergency patient care as established by the Thai Emergency Medicine Foundation in 2013 includes:

Code 1: Abdominal/back/pelvic and groin pain
Code 2: Anaphylaxis/allergic reactions
Code 3: Animal bites
Code 4: Bleeding (non-traumatic)
Code 5: Breathing difficulties
Code 6: Cardiac arrest
Code 7: Chest pain/cardiac pain
Code 8: Chocking
Code 9: Diabetes
Code 10: Environmental hazard
Code 11: Unassigned
Code 12: Headache/neck pain
Code 13: Psychiatric/behavioral issues
Code 14: Drug overdose/poisoning
Code 15: Obstetric/gynecological emergencies
Code 16: Seizures
Code 17: General Illness/Weakness (Non-specific)/Others
Code 18: Weak Limbs/difficulty speaking/facial droop (stroke)
Code 19: Unconscious/unresponsive/transient loss of consciousness
Code 20: Pediatric/emergency pediatric care
Code 21: Assault/injury
Code 22: Burns - thermal/electrical/chemical
Code 23: Drowning/water-related injuries
Code 24: Motor vehicle accidents
Code 25: Medical staff alert/vital signs abnormalities

Hospital staff shifts

Morning Shift: from 08:00 to 15:59
Afternoon Shift: from 16:00 to 23:59
Night Shift: from 00:00 to 07:59

Patient admission

Patients requiring hospitalization for at least 24 hours.

RESULTS

During the study period, 37,474 patients were screened for eligibility at the ED of Lampang Hospital. Of these, 17,344 were excluded: 712 based on intubation before triage, 39 died before arrival, 40 died in ER, 289 left against medical advice, 1,831 were referred to outpatient services, 71 refused treatment and 15,074 had incomplete data. Consequently, a total of 19,418 cases were included in the complete case analysis (Figure 1).

Although the initial sample size calculation indicated a need for 10,000 cases, data from 19,418 patients were collected to enhance robustness, increase statistical power, account for missing data, and ensure greater generalizability.

The study population consisted primarily of females, making up 59% of the total, with an average age of 49.9±0.2 years. Approximately half of the medical services were provided during the afternoon shift and two-thirds of the cases were non-trauma related. Over one-third of the patients were triaged as level 3 (Table 1).

Univariable and multivariable logistic regression analyses identified several predictors of hospital admission, including age, respiratory rate, pulse rate, blood oxygen level, temperature, GCS score, triage levels 1-3, and modes of transportation (e.g., referral, relatives, ALS, BLS, stretcher, wheelchair). Non-trauma patients and CBD codes 1, 4, 5, 7, 9, 10, 12-25 were also significant predictors (Table 2)

The admission model (see: supplementary materials) showed excellent performance with an AUROC of 0.8934. (95% CI, 0.8890-0.8980) (Figure 2). A calibration plot indicated high accuracy (E:O = 1.000) (Figure 3). Internal validation using bootstrapping confirmed the model's robustness with a C-statistic of 0.8920 and minimal shrinkage, indicating reliability when applied to other datasets (Table 3).

Risk curve analysis (Figure 4) identified optimal cutoff points for the probabilities of admission, leading to practical recommendations for patient management based on the chance of admission. The optimal cutoff points are at log odds = -1.1 and 0.45, corresponding to probabilities of admission of 25% and 60%, respectively. The calculated

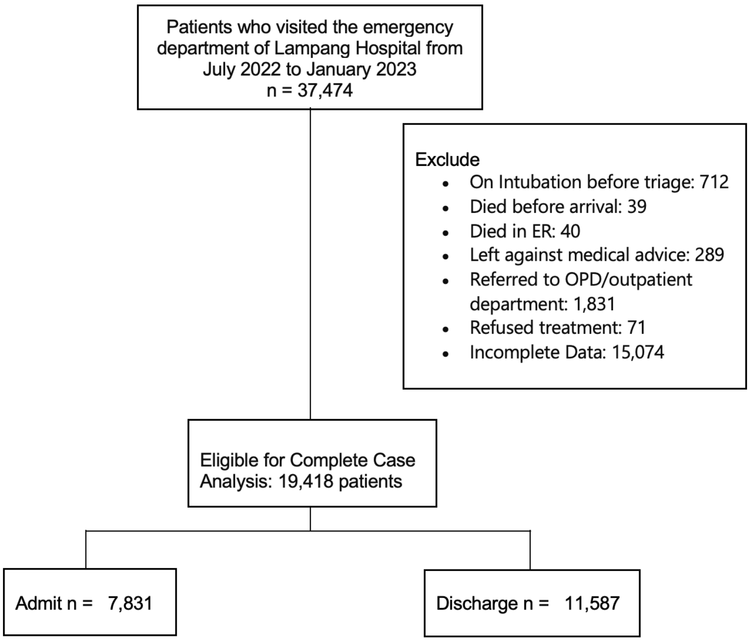

Figure 1. Outcome flowchart

percentages are used as follows (Table 4) 1) 0-25%: Can be discharged (false positive rate 3.8%, 2) 25%-60%: Consider consultation with an emergency medicine physician, 3) 60%-100%: Can be admitted (false positive rate 3.7%).

Decision curve analysis demonstrated that the admission model outperforms standard clinical judgment, showing substantial benefits from an admission prevalence of 10% and above. This study had a high prevalence of admission at 40.3%, indicating significant benefits (Figure 5).

DISCUSSION

The study identified critical predictors of hospital admission in the emergency setting, including age, respiratory rate, blood oxygen level, temperature, and GCS scores. These findings align with previous research by Kishore et al., which also highlighted the significance of these variables in predicting hospital admissions (12). Moreover, also in agreement other studies, patients triaged at levels 1-3 and those arriving via hospital transport such as referrals or emergency medical services (EMS) or by stretcher were more likely to be admitted (13-18).

Our study's methodology and the use of big data significantly contributed to the robustness of our findings. By nearly doubling the pre-calculated sample size needed and employing a complete case analysis, the data's reliability exceeded that typically achievable through methods that permit data imputation (19). The minimal amount of missing data and the predominance of clinical variables helped ensure comprehensive coverage and high validity of the study results (20).

The Admission Model's high AUROC values (0.8934) and accuracy further validate its effectiveness in clinical settings, outperforming traditional clinical judgment. These results are similar to those reported in other studies (21-24) in the region, which reported AUROC values ranging from 0.630 to 0.878, demonstrating the model's superior predictive capability.

Critically, the present study also carefully considered the balance between risks of over-discharge and excessive admission. The defined cutoff points were optimized to maintain false positive rates below 5%, which is essential for minimizing potential harm in clinical practice (25, 26). Over-admission, typically influenced by non-clinical factors such as relatives' preferences or specialist referrals, and over-discharge, particularly concerning for patients with chronic conditions who might manage at home, were notably low (27, 28).

The primary limitation of this research lies in its derivation of the admission model, which, while robust, represents only the initial stage in the development of Clinical Prediction Rules. The lack of external validation is a significant gap that

Table 1. Baseline characteristics of patients who visited emergency department, Lampang Hospital

Characteristics	Total (n=19,418)	Admission (n=7,831)	Discharge (n=11,587)	*p*-value
Female	11,457	4,582	6,875	0.070
Age (years), mean±SD	49.9±0.2	57.2±0.2	44.5±0.2	<0.001
Mean arterial pressure (mmHg), mean±SD	98.0±0.1	97.9±0.2	98.1±0.1	0.511
Respiratory rate (breaths per minute), mean±SD	20.3±0.02	21.4±0.10	19.5±0.00	<0.001
Pulse rate (beat/min), mean±SD	90.1±0.1	91.7±0.2	88.9±0.2	<0.001
SpO_2 (%), mean±SD	97.5±0.02	96.9±0.05	97.8±0.02	<0.001
Temperature (degree celsius), mean±SD	36.7±0.0	36.9±0.0	36.6±0.0	<0.001
Glasgow Coma score (sum), [min, max]	15 [3, 15]	15 [3, 15]	15 [6,15]	<0.001
Pain scale	2.3±0.02	2.1±0.03	2.4±0.03	<0.001
Shift, n (%)				<0.001
Morning (08:00 to 15:59)	7,091 (36.5)	3,035 (38.8)	4,056 (35.0)	
Afternoon (16:00 to 23:59)	9,679 (49.9)	3,709 (47.4)	5,970 (51.5)	
Night (00:00 to 07:59)	2,648 (13.6)	1,087 (13.8)	1,561 (13.5)	
Triage, n (%)				<0.001
Level 1	1,108 (5.7)	1,046 (13.4)	63 (0.5)	
Level 2	5,924 (30.5)	3,751 (47.9)	2,173 (18.8)	
Level 3	7,915 (40.8)	2,917 (37.2)	4,998 (43.1)	
Level 4	3,750 (19.3)	122 (1.4)	3,638 (31.4)	
Level 5	720 (3.7)	5 (0.1)	715 (6.2)	
Type, n (%)				<0.001
Trauma	6,653 (34.3)	2,270 (29.0)	4,383 (37.8)	
Non-trauma	12,765 (65.7)	5,561 (71.0)	7,204 (62.2)	
CBD, n (%)				<0.001
1. Abdominal/back/pelvic and groin pain	3,699 (19.1)	1,346 (17.2)	2,353 (20.3)	
2. Anaphylaxis/allergic reactions	209 (1.1)	14 (0.2)	195 (1.7)	
3. Animal bites	992 (5.1)	29 (0.4)	963 (8.3)	
4. Bleeding (nontraumatic)	205 (1.1)	135 (1.7)	70 (0.6)	
5. Breathing difficulties	1,332 (6.9)	943 (12.0)	389 (3.4)	
6. Cardiac arrest	12 (0.1)	5 (0.1)	7 (0.1)	
7. Chest pain/cardiac pain	843 (4.3)	363 (4.6)	480 (4.1)	
8. Chocking	15 (0.1)	5 (0.1)	10 (0.1)	
9. Diabetes	41 (0.2)	35 (0.4)	6 (0.1)	
10. Environmental hazard	97 (0.5)	29 (0.4)	68 (0.6)	
11. Unassigned	0 (0.0)	0 (0.0)	0 (0.0)	
12. Headache/neck pain	800 (4.1)	153 (2.0)	647 (5.6)	
13. Psychiatric behavioral issues	98 (0.5)	53 (0.7)	45 (0.4)	
14. Drug overdose/poisoning	61 (0.3)	48 (0.6)	13 (0.1)	
15. Obstetric/gynecological emergencies	75 (0.4)	38 (0.5)	37 (0.3)	
16. Seizures	263 (1.4)	247 (3.2)	16 (0.1)	
17. General illness/weakness (non-specific)/others	4,459 (23.0)	1,752 (22.4)	2,707 (23.4)	
18. Weak limbs/difficulty speak-ing/facial droop (stroke)	382 (2.0)	334 (4.3)	48 (0.4)	
19. Unconscious/ unresponsive/ transient loss of consciousness	137 (0.7)	85 (1.1)	52 (0.4)	
20. Pediatric/emergency pediatric care	276 (1.4)	62 (0.8)	214 (1.8)	
21. Assault/injury	220 (1.1)	67 (0.9)	153 (1.3)	
22. Burns thermal/ electrical /chemical	54 (0.3)	25 (0.3)	29 (0.3)	
23. Drowning/water-related injuries	14 (0.1)	6 (0.1)	8 (0.1)	
24. Motor vehicle accidents	3,380 (17.4)	1,213 (15.5)	2,167 (18.7)	
25. Medical staff alert/vital signs abnormalities	1,754 (9.0)	844 (10.8)	910 (7.9)	

CBD, criteria-based dispatch; GCS, Glasgow Coma Scale scores

Table 2. Univariable and Multivariable logistic regression

Parameter	Univariable logistic regression			Multivariable logistic regression		
	uOR	95% CI	*p*-value	mOR	95% CI	*p*-value
Female	1.02	1.01-1.03	0.502	1.01	1.03	0.500
Age (years)	1.03	1.03-1.03	<0.001	1.02	1.02-1.02	<0.001
Mean arterial pressure (mmHg)	0.99	1.00-1.00	0.511	1.00	0.99-1.00	0.002
Respiratory rate (breaths per minute)	1.24	1.23-1.26	<0.001	1.09	1.07-1.10	<0.001
Pulse rate (beat/min)	1.01	1.01-1.01	<0.001	1.00	1.00-1.00	0.002
SpO_2 (%)	0.90	0.89-0.91	<0.001	0.98	0.97-1.00	0.020
Temperature (degree celsius)	1.43	1.39-1.49	<0.001	1.26	1.19-1.33	<0.001
Glasgow Coma score (sum)	0.58	0.55-0.62	<0.001	0.84	0.79-0.91	<0.001
Pain Scale	0.96	0.95-0.97	<0.001	1.00	0.98-1.01	0.889
Shift						
Morning	1.20	1.13-1.28	<0.001	1.05	0.96- 1.15	0.299
Afternoon	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Night	1.12	1.03-1.22	0.011	1.04	0.93-1.17	0.488
Triage						
Level 1	2374.25	950.36-5931.50	<0.001	142.40	55.85- 363.08	<0.001
Level 2	246.84	102.27-595.81	<0.001	35.12	14.38-85.74	<0.001
Level 3	83.46	34.59-201.37	<0.001	17.25	7.09-42.00	<0.001
Level 4	4.40	1.79-10.82	0.001	2.05	0.83-5.07	0.120
Level 5	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Carrier						
Refer	136.06	111.42-166.14	<0.001	25.44	20.31-31.87	<0.001
Relative	4.22	3.72-4.78	<0.001	1.52	1.30-1.76	<0.001
ALS	45.26	34.12-60.05	<0.001	4.35	3.08-6.14	<0.001
BLS	14.09	12.16-26.32	<0.001	2.38	1.97-2.88	<0.001
Citizen	5.01	2.38-10.55	<0.001	1.15	0.44-3.01	0.772
FR	19.00	12.48-28.90	<0.001	2.46	1.54-3.93	<0.001
Friend	1.81	1.43-2.31	<0.001	1.26	0.95-1.66	0.113
Other	12.06	7.87-18.49	<0.001	2.81	1.66-4.77	<0.001
By yourself	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Transfer						
Relative	4.19	3.10-5.66	<0.001	1.78	1.22-2.60	0.003
Stretcher	13.40	12.26-14.65	<0.001	2.35	2.08-2.66	<0.001
Carry	9.58	4.90-18.72	<0.001	3.78	1.61-8.92	0.002
Walk	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Wheelchair	3.51	3.14-3.91	<0.001	1.43	1.25-1.64	<0.001
Type						
Trauma	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Non-trauma	1.49	1.40-1.59	<0.001	0.55	0.39-0.79	0.001
CBD						
1. Abdominal/back/pelvic and groin pain	19.00	13.05- 27.64	<0.001	5.20	2.90-9.33	<0.001
2. Anaphylaxis/allergic reactions	2.38	1.24-4.60	0.009	1.13	0.51-2.54	0.763
3. Animal bites	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
4. Bleeding (nontraumatic)	64.04	40.07-102.35	<0.001	12.14	6.16-23.91	<0.001
5. Breathing difficulties	80.50	54.62- 118.64	<0.001	4.77	2.61-8.71	<0.001
6. Cardiac arrest	23.72	7.10- 79.19	<0.001	3.73	0.93-15.04	0.064
7. Chest pain/cardiac pain	25.11	16.94-37.23	<0.001	3.36	1.84-6.13	<0.001
8. Chocking	16.60	5.34- 51.67	<0.001	1.07	0.21-5.52	0.939
9. Diabetes	193.71	75.55-496.64	<0.001	18.7	6.06-57.68	<0.001
10. Environmental hazard	14.16	8.01- 25.05	<0.001	4.89	2.22-10.80	<0.001
11. Unassigned	NA	NA	NA	NA	NA	NA
12. Headache/neck pain	7.85	5.22-11.82	<0.001	2.51	1.37-4.61	0.003
13. Psychiatric behavioral issues	39.11	22.73- 67.28	<0.001	10.89	5.11-23.22	<0.001
14. Drug overdose /poisoning	122.61	59.95-250.77	<0.001	39.10	16.77-91.16	<0.001
15. Obstetric/gynecological emergencies	34.10	19.01- 61.17	<0.001	11.45	5.18-25.33	<0.001
16. Seizures	512.63	274.07-958.85	<0.001	46.81	21.26-103.04	<0.001
17. General Illness/weakness (non-specific)/ others	24.49	14.78- 31.25	<0.001	5.10	2.85-9.11	<0.001

Table 2. Univariable and Multivariable logistic regression (continued)

Parameter	Univariable logistic regression			Multivariable logistic regression		
	uOR	95% CI	*p*-value	mOR	95% CI	*p*-value
CBD						
18. Weak limbs/difficulty speaking/facial droop (stroke)	231.06	143.34-372.47	<0.001	22.41	11.42-44.01	<0.001
19. Unconscious/ unresponsive/ transient loss of con-sciousness	54.28	32.74-89.99	<0.001	4.86	2.41-9.82	<0.001
20. Pediatric/emergency pediatric care	9.62	6.04-15.32	<0.001	5.85	2.97-11.51	<0.001
21. Assault/injury	14.54	9.11-23.22	<0.001	6.24	3.40-11.45	<0.001
22. Burns thermal/ electrical /chemical	28.62	14.94-54.84	<0.001	12.89	5.26-31.54	<0.001
23. Drowning/water-related injuries	24.91	8.12-76.42	<0.001	6.14	1.14-33.21	0.035
24. Motor vehicle accidents	28.59	12.76-27.07	<0.001	5.55	3.46-8.90	<0.001
25. Medical staff alert/vital signs abnor-malities	30.80	21.04-45.09	<0.001	7.06	4.35-11.47	<0.001

ALS, advanced life support; BLS, basic life support; CBD, criteria-based dispatch; FR, first responder, NA; not applicable

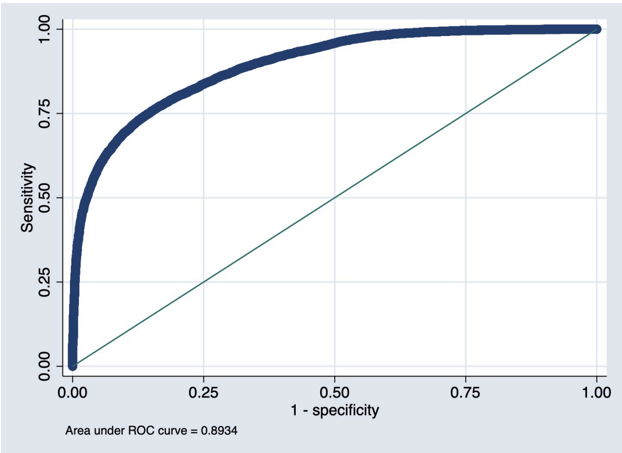

Figure 2. Area under the receiver operating characteristic (AUROC)

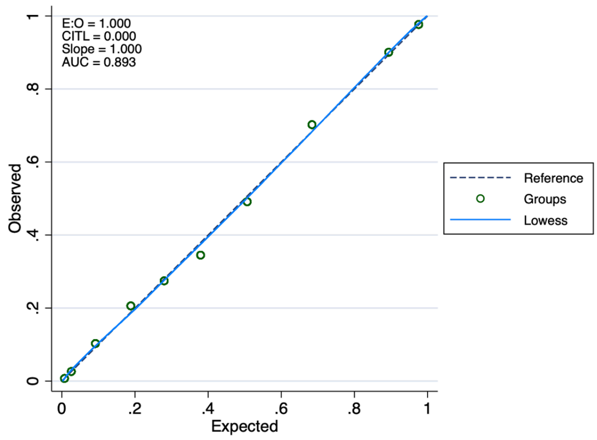

Figure 3. Calibration plot

Table 3. Bootstrapping method internal validation

	Apparent	95% CI	Boostrap	95% CI
Brier scaled	47.0		46.7	
C-statistic	0.8934	0.8890-0.8980	0.8920	0.8880-0.8950
E:O ratio	1.000		1.001	0.990-1.015
CITL	0.000	-0.039-0.039	-0.001	-0.045-0.037
Slope	1.000	0.970-1.030	0.990	0.964-1.021

Bootstrap shrinkage = 0.990; CITL, Calibration-in-the-large

Table 4. Percent of prediction compare true admit and true discharge

Decision	Percent of prediction	True admit (%)	True discharge (%)	Total (%)
Discharge	0-25%	748 (3.8)	7373 (38.0)	8,115 (41.8)
Consult	>25%-60%	2,198 (11.3)	3,488 (18.0)	5,686 (29.3)
Admission	>60%-100%	4,891 (25.2)	726 (3.7)	5,617 (28.9)
Total		7831 (40.3)	11,587 (59.7)	19,418 (100.0)

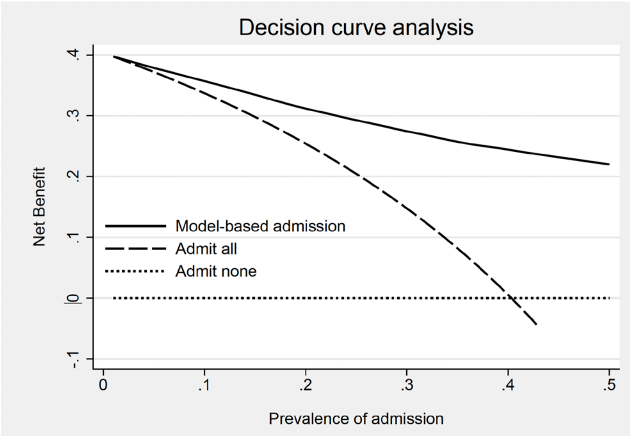

Figure 4. Decision analysis

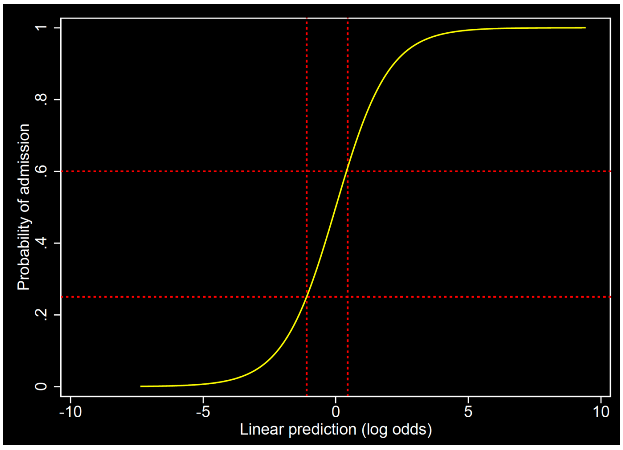

Figure 5. Risk curve

future work must address. Incorporating temporal and geographical validations can enhance the model's applicability and reliability across different settings and over time (29). However, there has been no external validation, nor has the model been implemented in clinical practice, and no comparable studies have previously been conducted in Thailand.

The focus of our study is to enhance the triage decision-making process by predicting the likelihood of hospital admission at the initial triage point using real-time electronic data. This focus was chosen to address the immediate need for improving both the accuracy and efficiency of initial triage decisions in the ED. While revisits and mortality among released patients are not specifically addressed in our study, we acknowledge that they have important consequences for patient safety and the standard of care. Patients who return to the ED frequently have untreated or deteriorating illnesses. For that reason, to avoid unfavorable outcomes, admission decisions should be carefully considered.

The exclusion of 15,074 patients due to incomplete data is acknowledged as a limitation; however, the impact on the study's findings may have been minimal given the large remaining sample size of 19,418 patients. This substantial dataset helps maintain the robustness and generalizability of our results despite the exclusions. The reasons for data incompleteness included operational issues and variations in documentation records. To address this limitation, we chose a complete case analysis approach to ensure the robustness of our predictive model. Future research should focus on enhancing data collection methods and developing strategies for effectively integrating incomplete datasets to minimize potential biases and to improve the comprehensiveness of research outcomes.

CONCLUSIONS

The hospital admission prediction model developed in this study demonstrated strong accuracy, with an AUROC of 0.8934. Key predictors include age, vital signs, and mode of arrival. The three-group cutoff system-discharge, consult, and admit-proved practical for real-time decision-making in the ED. While the model shows promise, external validation is necessary to confirm its broader applicability.

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All research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

CONFLICT OF INTEREST

There were no conflicts of interest regarding the publication of this paper.

ADDITIONAL INFORMATION

Supplementary materials

The following supporting information can be downloaded at: Appendix file

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Appendix

Admission Model

Sum of Log Odds (Linear combination)= -4.241326 + (3.981628*[(age/100)-0.4958559069])+(-2.215531*[(age/100)^2-2.458730804])+(-0.0052393*(map-98.00504686))+(0.00403*(pr-90.07482748))+(-2.121562*[(rr/10)^-2)-0.2430246143])+(-12.51323*[((rr/10)^-2)*ln(rr)-0.1718904041])+(-0.0185235*[spo2-97.45890411)+(0.2323003*[temp-36.72641364])+(-0.171473*[gcs_sum-14.79519003])+(0.0023636*[pain-2.285250798])+(-0.0078924*shift_morning)+(-0.482765*shift_noon)+(4.952123*triage_esi1)+(3.533679*triage_esi2)+(2.85074*triage_esi3)+(0.7189496*triage_esi4)+(0.2100244*carrier_2_friend+citizen)+(0.3701199*carrier_3_relative)+(0.8076558*carrier_4_bls,refer)+(1.41694*carrier_5_als)+(3.189861*carrier_6_refer)+(0.7382427*transfer_2_relative,carry)+(0.3750932*transfer_3_wheel)+(0.8891516*transfer_4_stretcher)+(-0.5363155*type_nontrauma)+(-1.409562*CBD_2)+(-1.474398*CBD_3)+ (0.9828423*CBD_4)+(0.0089316*CBD_5)+(-0.2241017*CBD_6)+(-0.3171437*CBD_7)+(-1.422221*CBD_8) + (1.465532*CBD_9) + (0.0789443*CBD_10) + (0.908997*CBD_13(12)) +(2.26813*CBD_14(13))+(0.9204234*CBD_15(14))+(2.332658*CBD_16(15))+(0.1096822*CBD_17(16))+(1.616454*CBD_18(17)+(0.0795744*CBD_19(18))+(0.5049024*CBD_20(19))+(0.3416289*CBD_21(20))+(1.077244*CBD_22(21))+(0.3703078*CBD_23(22)) +(0.2622904*CBD_24(23))+(0.4994029*CBD_25(24))

Odds = exp(Sum of Log Odds)

Probability = Odds/ (1+ Odds)

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Original Article **Open Access**

Feasibility of Large Multi-Leaf Collimator in Stereotactic Radiosurgery/ Stereotactic Radiotherapy: A Single Center Experience

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ABSTRACT

OBJECTIVE This study investigated the feasibility of using a large multi-leaf collimator (MLC) in a C-arm based linear accelerator for stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT).

METHODS Patient Specific Quality Assurance was conducted on 69 patients treated with a single lesion SRS/SRT measuring dose distribution using patient-specific plans with SRS MapCHECK®. Statistics were used to analyze the significance of correlation among dosimetric parameters, included Conformity Index (CI), Gradient Index (GI), plan complexity, and Gamma passing rate (GPR) in an absolute dose (AD) and relative dose (RD). confidence limit (CL) was also calculated to evaluate the performance of a large multileaf collimator (MLC) in SRS/SRT.

RESULTS Planning target volumes (PTVs) ranged between 0.34 cm^3 and 30.42 cm^3. The study found a value of CI_{ICRU}, CIPaddick, and GI of 1.29 ± 0.17, 0.77±0.10 and 5.24±2.18 (mean±SD), respectively, significant correlations were found between PTV sizes and dosimetric parameters. Values of $GPR_{2\%/2mm}$ were 92.42±3.74 (AD), 96.38±3.24 (RD), whereas $GPR_{2\%/1mm}$ were 82.03±6.69 (AD), 89.64±7.26 (RD). No significant correlation was found between plan complexity and GPR. CL values were 85.09% (AD), 90.03% (RD) for $GPR_{2\%/2mm}$ and 68.92% (AD), 75.41% (RD) for $GPR2_{\%/1mm.}$

CONCLUSIONS This study assessed the feasibility of using a large MLC for a single lesion SRS/SRT across various PTV sizes. The values of CI and GI decreased for a small lesion. While the large MLC performed adequately across different PTV sizes, the CL value of RD GPR at 2%/1 mm fell below 90%. This indicates that the contribution of PTV margin might be considered for a large MLC in SRS/SRT.

KEYWORDS stereotactic radiosurgery, stereotactic radiotherapy, multi-leaf collimator, dosimetric parameter, gamma analysis

INTRODUCTION

Radiosurgery is a specialized radiotherapy technique commonly employed as an alternative approach for treating intra-cranial lesions. This treatment technique is mostly employed in intra-cranial abnormalities, e.g., the vascular malformations, brain tumors and brain cancer, when the primary treatment method (surgical intervention) is not feasible. Two treatment techniques are encompassed in this treatment approach: stereotactic radiosurgery (SRS), which involves delivering a single large radiation dose to the target (1), and stereotactic radiation therapy (SRT) which administers a high radiation dose over multiple fractions. Due to the high radiation dose of the treatment, the size and volume of the target lesion are limited (range 1-35 cm^3) (2) to prevent complications from radiation that can occur in nearby normal tissue. The American Association of Physicists in Medicine no. 54 (3) (AAPM no. 54) released a guideline on this treatment technique which emphasized not only the accuracy of delineation but also the rapid falloff of the outside radiation dose. Delineation accuracy was improved by utilizing image registration among multiple modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Various other treatment modalities have been employed in this technique, including Gamma Knife® (4), C-arm based linear accelerator (5, 6) C-arm linac, tomotherapy (7-9) and CyberKnife® (10).

AAPM no. 54 is not limited to specific treatment modalities. A C-arm Linac is widely used as a radiosurgery technique. This machine can benefit from being equipped with various aperture devices for SRS/SRT (2, 11-13) such as cylindrical collimators (CC), mini multi-leaf collimators (mMLC), multi-leaf collimators (MLC), etc. Currently, the use of mMLC and MLC is widespread because the shape variation of the machine aperture. This provides advantages in the performance of the treatment technique in photon fluence modulation, e.g., intensity modulation radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). These sophisticated techniques can control the conformity of the radiation volume on the target and can also provide a high dose gradient outside the target as well. However, the width of the MLC may impact the delivered dose distribution to the lesion, particularly a small target. Larger MLCs have a wider leaf, which can reduce precision in shaping the radiation beam to the target contours which can lead to a less conformal dose distribution. Additionally, larger MLCs create a wider penumbra, the region at the edge of the radiation field where the dose rapidly falls off. This penumbra can result in less high dose gradients, reducing the precision of dose confinement to the target and potentially increasing the dose to surrounding healthy tissues. The recommendation for mMLC of less than 5 mm leaf width might be beneficial for a small target volume (12). Although the use of mMLC is suitable for a radiosurgery, its use might be limited in a clinical practice, e.g., the treatment of a large target. The performance of large MLCs (5 mm leaf width) has been compared to a mMLC (14-20). Although a small MLC provided better dosimetric parameters (15, 16) than a large MLC such as the conformity index (CI) and gradient index (GI), no significant difference was found between these two sizes of MLC (14, 17-20).

CI is the most significant dosimetric parameter in the plan quality of radiosurgery. Many publications (14, 17-20) have found no significant differences in this parameter among different MLCs. Utilizing a large MLC, a decreasing value of CI according to The International Commission on Radiation Units and Measurement (CI_{ICRU}) (21) or an increasing value of CI according to Paddick ($CI_{Paddick}$) (22) is observed when the volume of the target is increased (19, 23). This evidence may not only impact the plan qualities (16, 20, 24) but also the delivered dose in a treatment. With a large width MLC, achieving a high CI becomes challenging, which means the radiation dose is less well confined to a small target volume. This can compromise the effectiveness of the treatment and increase the risk of side effects. The use of large MLCs also requires experimental dosimetric procedures using Patient Specific Quality Assurance (PSQA) including protocols for verifying that the delivered dose distribution matches the planned dose distribution as measured by gamma analysis. The objective is to assess the feasibility of using large MLCs in intra-cranial single lesion stereotactic radiosurgery techniques by evaluating dosimetric quality parameters and conducting gamma analysis.

METHODS

Patient Selection and Treatment Planning

This retrospective study recruited patients with a single brain lesion between January 2019 and December 2023. The sample size of 69 patients was calculated using the Danial formula (25). The sample included 41 males and 28 females with a median age at 45 years (range 9-76 years).

All selected patients underwent a CT Simulator (SOMATOM Definition AS, Siemens Healthineers, Forchheim, Germany) with a slice thickness of 1 mm. Patients were immobilized using a specific thermoplastic mask for SRS/SRT techniques. The CT images set was registered with MRI images with T1-weighted for a delineation (target and normal structures). The Planning Target Volume (PTV) was expanded by 1-2 mm from the Gross Target Volume (GTV). In this group of patients, 23 cases were treated with the SRS, and 46 cases underwent the SRT. The treatment plans were created by the MONACO® treatment planning system (TPS) version 6.1.3.0 (Elekta, Stockholm, Sweden) using the Monte Carlo Algorithm Calculation. All treatment plans calculated the dose using a grid size of 1-2 mm. The geometrical radiation beam included 3-5 non-coplanar arcs with the VMAT technique using 6 MV photons. The MLC of the C-arm Linac (Synergy®, Elekta, Stockholm, Sweden) was upgraded by replacement with a 5 mm MLC leaf width. Before delivery, the position was verified by using a cone beam CT system and was corrected by the 6 degrees of freedom couch. This study was approved by Ethics Committee of Chiang Mai University on 19 Nov 2023 (study code: RAD-2566-055).

PSQA preparation and Gamma analysis

PSQA was conducted using the SRS MapCHECK® (SRSMC) (Sun Nuclear Co., Melbourne, FL, USA). This device has been used in clinical practice since September 2023. The SRSMC consists of an inserted 2D diode array in a Sun Nuclear StereoPHAN®, a polymethyl methacrylate cranioplasty (PMMA) material with a cylindrical shape and one round end (SRS phantom system) (Figure 1A). The beam geometries of the treatment plan were transferred onto this phantom system. Although the non-coplanar technique is employed in clinical practice, this study designed the beam geometries with zero degrees of couch and gantry angle arrangement as illustrated in Figures 1B and 1C. The PSQA plan dose distribution was then recalculated using a 1 mm resolution and exported to SNC Patient software version 8.5 (Sun Nuclear

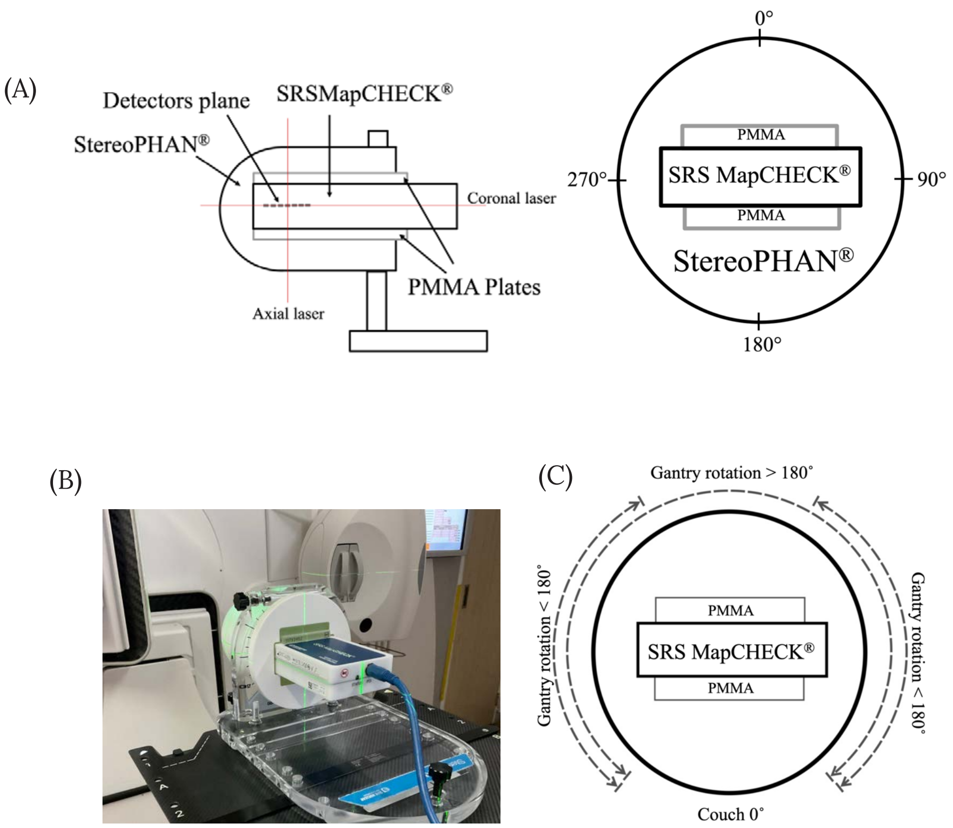

Figure 1. Diagram and phantom setup position. (A) SRS phantom diagrams, (B) SRS phantom setup, (C) Gantry angles arrangement in the PSQA treatment planning

Co., Melbourne, FL). For the dose measurement, a surface guided radiation therapy (SGRT) system (Catalyst HD® system, C-RAD®, Uppsala, Sweden) was employed to ensure the delivery set-up position. The PSQA measurement method utilized a true composite at zero degrees of couch.

Dosimetric parameters and evaluation tools

Various dosimetric parameters were utilized to assess the feasibility of a large MLC in SRS/SRT including the CI_{ICRU} (21), $CI_{Paddick}$ (22), GI (26), modulation factor (MF) (27), and the fluence map variations (FMV). The FMV was calculated using the standard deviation (SD) provided by the TPS. This system reported a photon fluence of leaf template summation per arc gantry as illustrated in Figure 2. The SD of the fluence can represent the plan complexity without having an impact on the scatters in the monitor unit calculation. The formulas and ideal values of these dosimetric parameters are described in Table 1. To evaluate the Gamma analysis, the results of PSQA plans across various PTV sizes were analyzed using the Gamma criteria (28) at 2%/2 mm and 2%/1 mm, with a 10% low dose threshold. The Gamma passing rate (GPR) was calculated both with an absolute dose (AD) and with a relative dose (RD). The standard guideline recommends this value should not be below 95% for a complex treatment plan (29).

Confidence limits (CL)

The confidence limits value represents the plan quality assurance in each center and was determined by the formula of the AAPM TG119 recommendation as shown in Table 1. The formula is expressed as $(100 - \text{mean}) + 1.96\sigma$, where the mean is the average value of the GPR and σ is the SD of that value. A value might increase or decrease depending on various factors such as the implementation of new treatment techniques and measuring devices, new staff orientation, etc. Although there were no recommended passing criteria of CL, our center agreed that the CL value should not be below 90%. The performance of the large MLC in SRS/SRT was also accessed using this parameter as well.

Statistical analysis

Significant correlations were investigated among different sizes of PTV, dosimetric indexes,

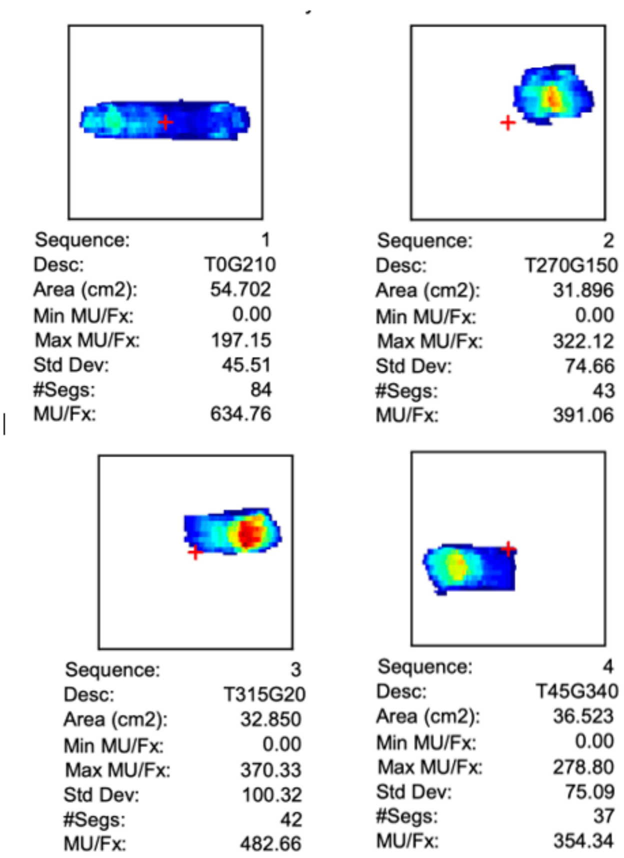

Figure 2. Characteristics of photon fluence in each gantry arc per treatment plan where sequence is the number of gantry arc

Table 1. Mathematical definition of dosimetric parameters

Dosimetric index	Definition	Ideal value	References
Conformity index			
ICRU	CI_{ICRU} = PIV / PTV	1	ICRU (21)
Paddick	$CI_{Paddick}$= TV_{PIV}^2 / (PTV × PIV)	1	Paddick (22)
Gradient index	GI = $PIV_{50\%}$/ $PIV_{100\%}$	As low as possible	Paddick and Lippitz (26)
Modulation factor	MF = MU/Dose	-	Chiavassa et al. (27)
Fluence map variation	FMV = $\sigma_{photon\ fluence}$ /dose	-	-
Confidence limits	CL=(100-mean)+1.96σ	*Remark	AAPM TG-119 (30)

*Remark: should be as much as possible or depend on the individual treatment center agreement.
CI_{ICRU}, conformity index of ICRU; PIV, prescribed isodose volume; PTV, planning target volume; $CI_{Paddick}$, conformity index of paddick; TV_{PIV}, treated volume of PIV; GI, gradient index, $PIV_{50\%}$, volume of 50% isodose level of the prescribed dose; $PIV_{100\%}$, volume of prescribed dose; MF, modulation factor; MU, monitor unit; FMV, fluence map variation; σ, standard deviation; CL, confidence limits.

Table 2. Mean value±standard deviation of various sizes of PTV, dosimetric parameters, and treatment plan complexity

Range of PTV (cm^3)	Number of cases	PTV (cm^3)	CI_{ICRU}	$CI_{Paddick}$	GI	MF	FMV
x ≤ 5.0	32	2.16±1.27	1.40±0.19	0.71±0.10	6.94±2.07	3.09±0.64	0.09±0.03
5.0 < x ≤ 10.0	14	6.59±0.98	1.23±0.06	0.81±0.04	4.36±0.47	3.26±0.62	0.09±0.02
10.0 < x ≤ 15.0	7	12.55±1.40	1.17±0.07	0.87±0.02	3.49±0.43	3.91±0.77	0.12±0.01
15.0 < x ≤ 20.0	7	17.20±1.29	1.15±0.04	0.85±0.05	3.30±0.18	3.43±0.82	0.11±0.03
20.0 < x	9	25.56±3.31	1.19±0.09	0.83±0.07	3.44±0.71	4.15±1.37	0.12±0.05
Total	69	8.69±8.38	1.29±0.17* ($p < 0.001$)	0.77±0.10* ($p < 0.001$)	5.24±2.18* ($p < 0.001$)	3.38±0.87* ($p = 0.002$)	0.10±0.03* ($p < 0.001$)

*Significant correlation between PTV sizes and parameter
PTV, planning target volume (x); CI_{ICRU}, conformity index of ICRU; $CI_{Paddick}$, conformity index of paddick; GI, gradient index; MF, modulation factor, FMV, fluence map variations

plan complexity and GPRs. Statistical significance was analyzed using Spearman's correlation with a confidence interval of 95% ($p < 0.05$) indicating statistical significance. The analysis was conducted using SPSS version 29.0.2.0 (IBM Co., Armonk, New York, USA).

RESULTS

Correlations among PTV, CI, GI and treatment plan complexity

This study involved different sizes of PTV ranging from 0.34 to 30.42 cm^3 with a mean volume of 8.69±8.38 cm^3 (mean±SD). The size of PTV was classified into 5 groups as illustrated in Table 2. The smallest size (volume < 5 cm^3) was 46.38% while for the 5-10 cm^3 size it was 20.28% of a total number of samples. The size that had a volume larger than 10 cm^3 was 33.34%. Table 2 demonstrates not only the characteristics of PTV but also other parameters and indices. The values of CI were 1.29±0.17 and 0.77±0.10 for the ICRU and Paddick, respectively. These results showed a moderately significant correlation ($p < 0.001$) between the PTV sizes versus CI_{ICRU} (r = -0.676) and the PTV sizes versus $CI_{Paddick}$ (r = 0.670). The mean GI had a value of 5.24±2.18, and a significant negative correlation (r = -0.913, $p < 0.001$) with PTV size. The complexity values of the treatment plan were 3.38±0.87 and 0.10±0.03 for the MF and the FMV, respectively. There was a low but statistically significant correlation between the PTV sizes and MF (r = 0.363, $p = 0.002$) and between PTV sizes and FMV (r = 0.444, $p < 0.001$).

Gamma passing rate and its correlation

This study employed the SRSMC to measure the GPR. Table 3 shows that the criterion at 2%/2mm had values of 92.42±3.74 and 96.38±3.24 for AD and RD GPR, respectively. The study also observed a tightened distance-to-agreement (DTA) with the criterion set at 2%/1 mm. This criterion had values of 82.03±6.69 and 89.64±7.26 for the AD and RD GPR, respectively. Significant correlations were observed for the following: r =

Table 3. Mean value ± standard deviation of various sizes of PTV, gamma passing rate, and confidence limits

Range of PTV (cm^3)	Number of cases	PTV (cm^3)	GPR 2%/2mm (%)		GPR 2%/1 mm (%)	
			AD	RD	AD	RD
x ≤ 5.0	32	2.16±1.27	93.32±3.03	97.06±2.93	82.60±6.10	91.47±5.89
5.0 < x ≤ 10.0	14	6.59±0.98	91.11±2.81	96.45±2.53	79.56±6.06	89.78±5.62
10.0 < x ≤ 15.0	7	12.55±1.40	91.83±5.06	94.73±4.40	81.29±7.34	85.54±10.33
15.0 < x ≤ 20.0	7	17.20±1.29	92.20±4.11	94.80±3.81	83.31±7.23	84.97±10.29
20.0 < x	9	25.56±3.31	91.93±5.66	96.33±3.73	83.57 ±8.87	89.73 ±7.43
Total	69	8.69±8.38	92.42±3.74* (p = 0.011)	96.38±3.24 (p = 0.752)	82.03±6.69 (p = 0.086)	89.64±7.26* (p = 0.034)
Confidence limits			85.09	90.03	68.92	75.41

*Significant correlation between PTV sizes and parameter
PTV, planning target volume (x); GPR, gamma passing rate; AD, absolute dose; RD, relative dose

-0.304 (p = 0.011) for PTV size versus AD GPR at 2%/2 mm, and r = -0.256 (p = 0.034) for PTV size versus RD GPR at 2%/1 mm. No significant correlations were found between PTV size and RD GPR at 2%/2 mm or AD GPR at 2%/1 mm. No significant correlations were found between GPR and GPR and complexity or between either MF, FMV and GPR.

Confidence limit (CL)

The CL was calculated based on overall GPR (Table 3). With a large MLC in the SRS/SRT, the CL revealed a value of 85.09% and 90.03% for the AD and RD GPR, respectively, using the criteria of 2%/2 mm. With tightened DTA, the results revealed values of 68.92% and 75.41% for the AD and RD GPR, respectively.

DISCUSSION

This study investigated the feasibility of using a 5 mm MLC leaf width in SRS/SRT for various PTV sizes by analyzing dosimetric parameters, plan complexities and GPRs.

Correlations among planning target volume, conformity index, gradient index, and treatment plan complexity

In terms of dosimetric parameters, the dose coverage of the target by CI assesses whether the prescribed dose conforms to the shape and size of the target volume. To observe the impact of CI and PTV sizes, these two parameters were plotted as illustrated in Figure 3. The trend line, a power function, reveals that both CI_{ICRU} and $CI_{Paddick}$ were improved when the PTV sizes were increasing. These results confirm the work of Dhabaan et al. (31) and Li et al. (32) Obviously, a large width of MLC might limit the ability to achieve optimal dose conformity, particularly for a small PTV. With a large width, it can be difficult to modulate the intensity precisely around a small target, resulting in less conformal dose coverage on the target. This impact was observed not only in this study but also in the work of Li et al. (13), Jalbout et al. (33) and Watcharawipha et al. (9,34)

Additionally, the GI is an important factor that represents the dose falloff in the surrounding normal tissue of the SRS/SRT. A low value of GI indicates not only a steep dose falloff outside the target but also good sparing of surrounding tissue. Figure 4 shows a steep dose gradient that was improved (decreasing GI value) as the PTV sizes were increased. This result aligns with previous studies by Ohtakara et al. (35) and Popple et al. (36) A large width of MLCs might produce broader penumbra regions, leading to less steep doses in a small lesion. That limitation could be more pronounced where precise dose distribution is critical. This observation confirms the work of Menon et al. (37) and Desai et al. (38)

The complexity of a radiation treatment plan was defined by the MF which is the ratio between the MU and the fraction dose. An increase in MU in the same beam geometry can indicate the complexity level of each plan, i.e., a high MF value indicates a high treatment planning complexity. Figure 5A shows the treatment plan complexity in terms of MF, which escalates with an increase in the PTV size. This result is consistent with the study of Li et al. (39) Additionally, the present study introduced an in-house evaluation tool, the FMV. The limitation of the MF may be due to MU

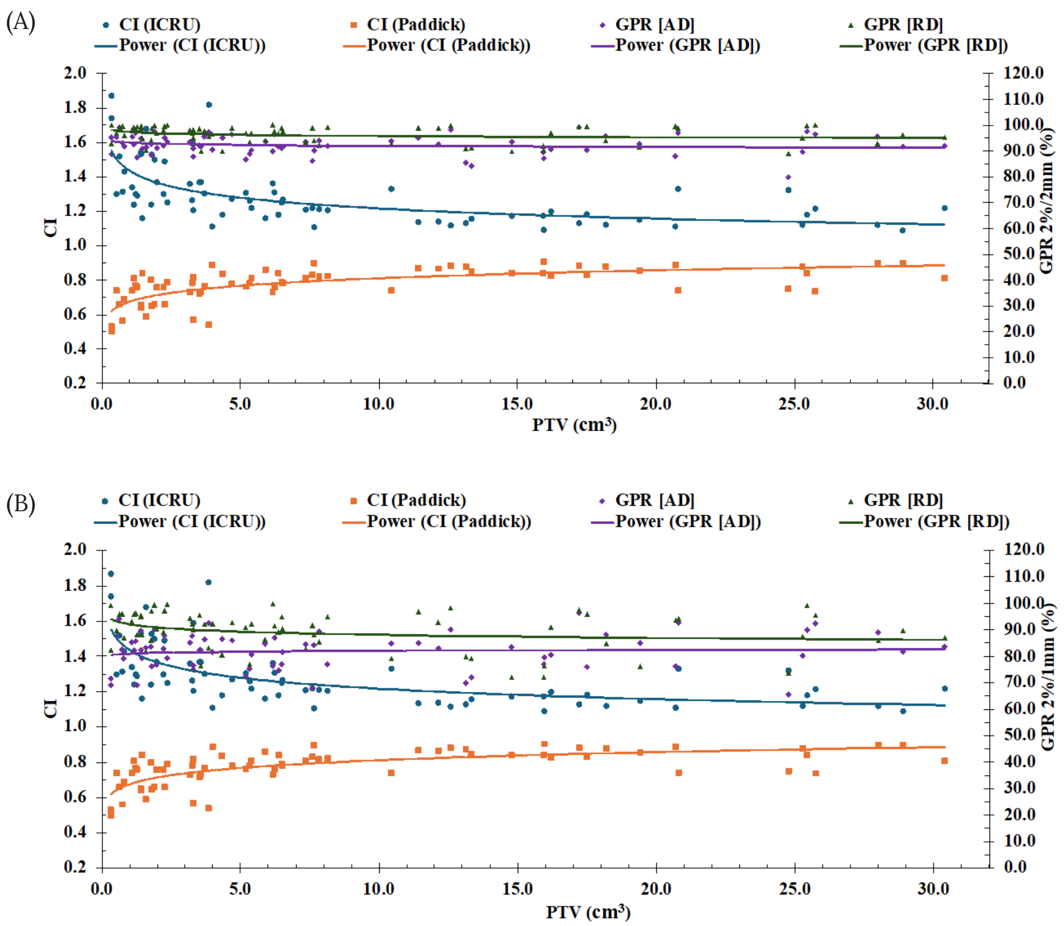

Figure 3. Plots and trend lines among various planning target volume (PTV) sizes, conformity index (CI), gamma passing rate (GPR): GPR 2%/2mm (A) and GPR 2%/1mm (B).

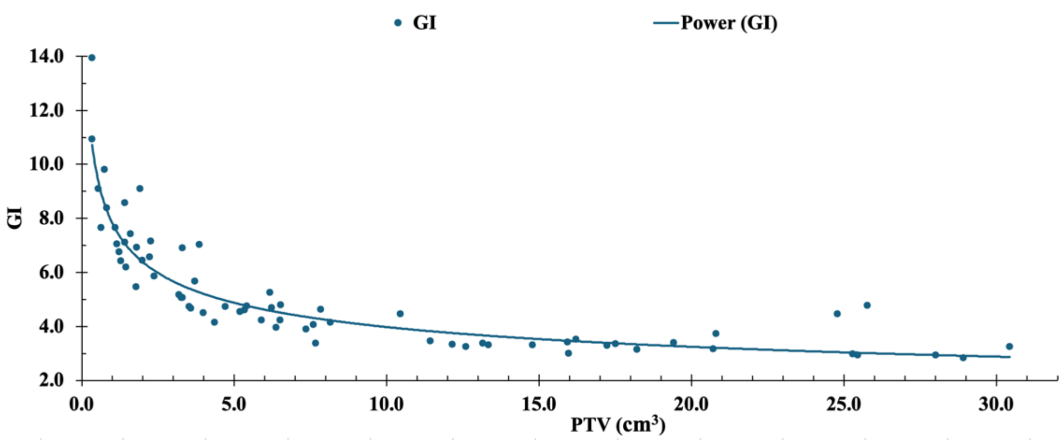

Figure 4. Plots and trend lines with various planning target volume sizes and gradient index

calculation in a small field size. This value may increase due to a lack of photon scatter in a small field size, even if the photon fluence was equal to a larger field size. The FMV may more accurately represent plan complexity than the MF due to variations in photon fluence. Figure 5B clearly demonstrates the high complexity of the treatment plan in terms of FMV for a large PTV.

Gamma passing rate and its correlation

In the PSQA, the beam geometries were designed with a zero-degree couch angle in this study. These geometries aimed to eliminate phantom position uncertainty caused by couch

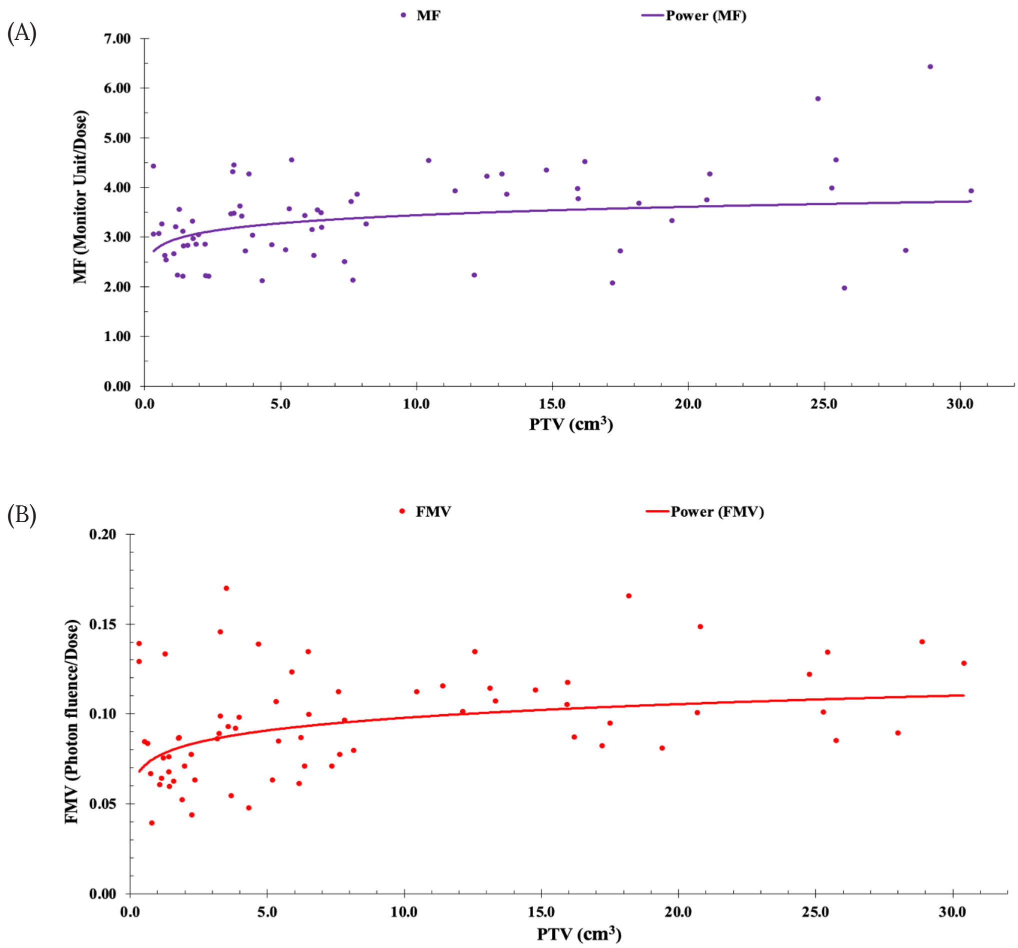

Figure 5. Plots and trend lines with various planning target volume (PTV) sizes, modulation factor (A) and fluence map (FM) variations (B).

rotation. Although the value of GPR differed between couch rotation and no couch rotation, no significant difference was found in either the AD (p = 0.313) or RD (p = 0.429).

In this study, the GPR value of 2%/2 mm was more than 90% higher than the GPR at 2%/1 mm. The GPR value decreased when tighter criteria were applied. Although the margin of PTV was calculated based on the uncertainty of the patient setup, this error could be reduced by image guided radiation therapy (IGRT) or SGRT. This clearly shows that the impact on the PTV margin remained. The margin could thus be attributed to 2 mm, particularly the impact of a large MLC in SRS/SRT. The correlation was observed between plan complexity and not only the AD GPR but also the RD GPR. Due to the variation in output of the Linac, the RD GPR closely represented the shape of the treatment planning dose distribution. In this study, the AD provided a lower value than the RD which indicates that the machine output impacted the GPR evaluation. This can be clearly observed in the AD GPR at 2%/1mm. The AD measurement showed a lower value while the RD value was similar to the other PTV groups. Figure 6 shows the GPR increasing simultaneously with decreasing plan complexity. This result confirms the work of Chiavassa et al. (27)

The dose distribution in terms of dosimetric plan quality was assessed. The results showed that the CI and GI impacted a small PTV size but improved for a larger PTV size. However, in terms of the PSQA, a large MLC was able to shape the beam precisely for a small PTV size. This is shown in Figure 3, which illustrates a slight impact on the GPR value with increasing PTV size. It also demonstrates that a large MLC enhances the precision of delivery of planned dose distributions. The VMAT was the technique that delivered a small beamlet to the target. Ability to limit the size of each beamlet depended on the treatment machine. Accuracy of MLC positions could

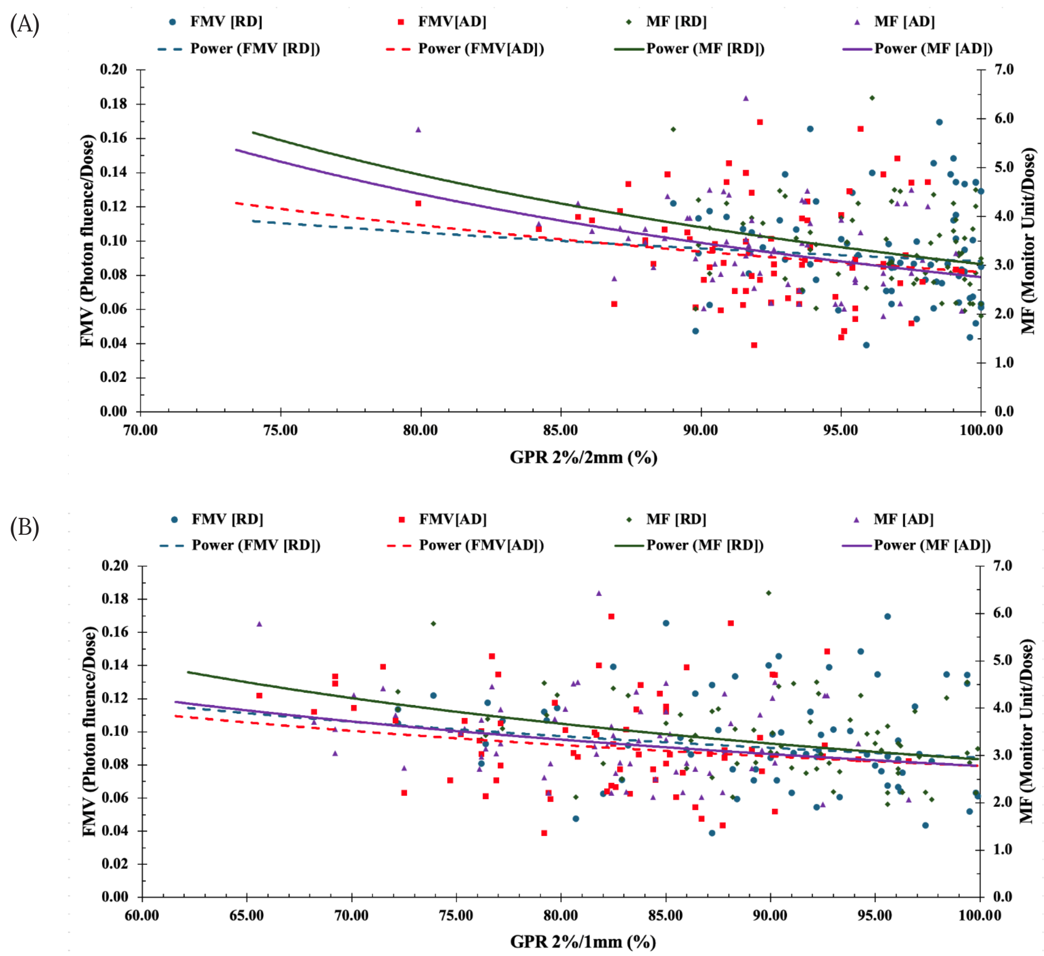

Figure 6. Plots and trend lines among various gamma passing rates (GPR), fluences map variations (FMV) and modulation factor (MF). GPR 2%/2mm (A) and GPR 2%/1mm (B)

be achieved, but at the cost of a trade-off in the CI value, particularly in the case of a small target. Statistical analysis found no significant correlations between plan complexity and GPR. The PTV size did not impact the GPR value, although increasing the size led to greater plan complexity. This demonstrates that a large MLC is effective in terms of increasing treatment plan complexity.

Confidence limit

The CL was used to ensure the level of treatment planning accuracy. Although there was a recommended GPR level (29), the level of CL had to be determined for each center. This study illustrates that a large MLC might cause a large SD in the GPR. These results demonstrated a low CL value when compared to studies with a small MLC in this treatment technique (40, 41). The variation in radiation output is one factor that can cause a wider range of SD values, particular the AD. Therefore, the AD may not be suitable for CL estimation compared to RD (29). Although there was a guideline on the tolerance limit value of the GPR, it was not on the CL. Our center then setup a tolerance limit for the CL that it should not be below 90% for the RD GPR at 2%/2 mm.

This study aimed to investigate the feasibility of using a large MLC in SRS/SRT. The investigation found the considerations of utilization in terms of the CI, GI, MF, FMV and GPR, that were against the PTV size. The results found a significant correlation between PTV size and all dosimetric parameters with the exception of RD GPR at 2%/2mm and AD GPR at 2%/1mm. This might be an issue when employing MLC in a small lesion as it would decrease the plan qualities of the CI and GI. Although plan complexity was significantly correlated with the PTV size, the MLC was able to achieve a satisfactory performance as indicated by the value of GPR. However, the GPR is one factor to consider when applying the 2%/1 mm criterion. The setup margin should be taken into account when using this size of MLC. Multiple lesions, however, present an interesting area for future research.

CONCLUSIONS

This study investigated the feasibility of a large MLC with various PTV sizes for a single lesion in the SRS/SRT. The study identified factors that should be considered when utilizing this size of MLC. The plan qualities of the CI and GI decreased when a large MLC was applied in a small lesion. Although this size of MLC can achieve a satisfactory performance with various PTV sizes, the CL value of RD GPR at 2%/1mm was found to be below 90%. Another consideration is that the setup margin could be contributing 2 mm in the PTV.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

A.C.: Conceptualization, data curation, investigation, formal analysis, writing–original draft, writing–review and editing; A.W.: conceptualization, formal analysis, writing–review and editing, Supervision; W.N.: formal analysis, writing–review and editing; A.K., B.J.: formal analysis.

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Original Article

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A Diagnostic Clinical Prediction Rule for Predicting Hip Subluxation/ Dislocation in Patients with Cerebral Palsy

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ABSTRACT

OBJECTIVE Hip subluxation/dislocation, a common problem in patients with cerebral palsy (CP), needs to be diagnosed with hip radiography. However, patients with cerebral palsy in a rural or country border areas may not have access to a radiographic screening program due to transportation difficulties and cost. This study aims to develop a clinical prediction rule (CPR) for diagnostic prediction of hip subluxation/dislocation in patients with CP for use as a risk-screening tool.

METHODS This is a cross-sectional diagnostic CPR development study. Data were obtained from medical and radiologic records of patients with CP who had undergone outpatient follow-up at a 750-bed general hospital between January 2017 and December 2023. Clinical predictive factors were medical records plus hip subluxation/dislocation diagnoses using the migration percentage (MP), with ≥ 33% indicating hip subluxation and ≥ 90% indicating hip dislocation. Multivariable logistic regression analysis was used for choosing predictive variables and rating their coefficient. Both discriminative and calibration aspects of the performance of the CPR were evaluated using both a development and an internal validity model.

RESULTS Among the 69 patients with CP in the study, the mean (SD) age was 113 (242) months. Of the 69 patients, 30 were diagnosed with hip subluxation/dislocation, a prevalence of 43%. Using multivariable logistic regression analysis, a simple CPR performance calibration system was developed which included three factors: age ≥ three years (1 point), female sex (1 point), non-ambulatory status (Gross Motor Function Classification System (GMFCS) levels IV and V) (2 points). The discriminative ability of the CPR, evaluated using the area under the receiver operating characteristic curve (AuROC), was 0.776 (95%CI: 0.668-0.884) and the calibration curve showed acceptable performance in both the development and the internal validation models.

CONCLUSIONS Our diagnostic CPR for predicting hip subluxation/dislocation in patients with CP provides acceptable discriminative and calibration performance. This CPR may be used to evaluate the risk of hip subluxation/dislocation in settings where hip radiography is not available. Further external validation studies are needed to confirm the robustness of the performance before applying this CPR in other clinical settings.

KEYWORDS cerebral palsy, hip subluxation, hip dislocation, clinical prediction rule

INTRODUCTION

Hip subluxation/dislocation is an important complication in patients with cerebral palsy (CP). The prevalence of hip subluxation/dislocation is reported to be 25-60%, depending on the country of origin, the individual's characteristics, and the specific hip surveillance program used with the cohort (1-3). For Thailand, the prevalence of hip subluxation/dislocation reported by the Queen Sirikit National Institute of Child Health is 57% (4). It should be noted that this prevalence may be different from that of other health facilities in Thailand where no formal hip surveillance program has been implemented.

Hip subluxation/dislocation can be diagnosed using the Reimers migration percentage (MP). The MP is calculated from the distance between the lateral border of the femoral head and Perkin's line (A) divided by the distance between the medial and lateral borders of the femoral head as presented in a plain radiograph of the hip then converting the value to a percentage (5, 6) (Figure 1). Hip subluxation will be diagnosed if the MP is > 33% but < 90%, whereas hip dislocation will be diagnosed if the MP is ≥ 90%. Patients who have MP > 33% should be referred to an orthopedist for proper management, including close observation, preventive programs such as botulinum toxin injection, physiotherapy and surgical intervention (6, 7). Previous studies have demonstrated that several factors can prognose an event of hip subluxation/dislocation, including age (2), female sex (8), Gross Motor Function Classification System (GMFCS) level (2), bilateral spastic hemiplegic type of CP (9), initial MP (10, 11), and initial head-shaft angle from hip radiography (11).

Although hip radiography is the best tool for detecting hip subluxation/dislocation, not all patients with CP can access a radiography facility, especially those who live in rural or border areas of middle- or low-income countries which have very limited health care system resources as well as limited public transportation (12). These patients may only be able to access health services at community-level clinics in mountainous areas or temporary clinics at country borders which have no radiographic facilities. Transportation of patients with CP from these areas can be expensive and difficult. For that reason, it is important to be able predict whether these patients have a risk of hip subluxation/dislocation or not before sending them to a hospital which can confirm a diagnosis of hip subluxation/dislocation using hip radiography.

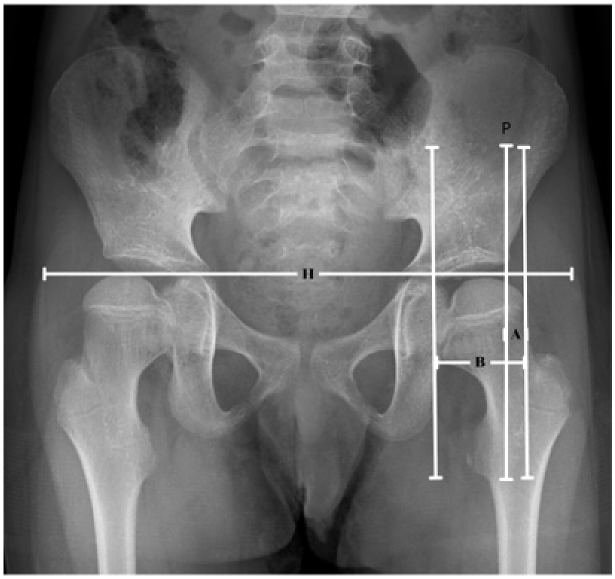

Figure 1. Migration percentage measurement

Determining predictive risk is to create a clinical prediction rule (CPR) which does not involve hip radiography (13). Instead of clinicians in areas lacking access to radiography having to depend on a single predictive factor or to have to deal with a difficult equation, CPR uses a set of predictive factors to determine the probability of the outcome by using a simple, ready-to-use scoring method (13). The CPR most frequently used in clinical settings is the APGAR score which is designed to predict the risk of birth asphyxia in newborns. However, to the best of our knowledge, there have been no studies about developing CPR for diagnostic prediction of hip subluxation/dislocation in patients with CP. The aims of this study are: 1) to report the prevalence of hip subluxation/dislocation in a general hospital which has no formal hip surveillance program, and 2) to develop a clinical prediction model for diagnosing hip subluxation/dislocation in patients with CP using data available at a general hospital that has no formal hip surveillance program.

METHODS

This is single-center, retrospective cohort study was conducted in an outpatient rehabilitation setting at a 750-bed general hospital. Data were obtained by reviewing electronic and written medical records of children with CP who had undergone outpatient follow-up at the hospital between January 2017 and December 2023. Clinical and radiographic data of all participants were obtained on the day of the follow-up.

Participants

The inclusion criteria for this study were: 1) having been diagnosed with spastic CP and 2) age between 0-15 years. The exclusion criteria were: 1) incomplete medical data of hip subluxation status at the time of the first follow-up; and 2) being diagnosed with postnatal CP since patients with postnatal CP follow different courses and have different prognoses from those with congenital CP (5). Therefore, we decided to exclude patients with postnatal CP to increase the internal consistency of the study population.

Predictive variables

Pre-specified independent variables of hip subluxation were obtained from participants' medical records, including: 1) age at the onset of CP (months), 2) age at the time of assessment (months), 3) sex (male/female), 4) anatomical subtype of CP (quadriplegia/diplegia/hemiplegia), and GMFCS level (ranging from 1 [walking without limitation] to 5 [limitation in head and trunk antigravity control]) (2).

Outcome variable

The outcome variable was the hip subluxation status evaluated by hip radiography. Radiographic imagings of all participants were extracted from the picture archiving and communication system (PACS). Radiographic imagings were investigated on the affected side for participants with hemiplegia and both sides for participants with diplegia and quadriplegia. All hip radiography investigation was done with the patient in a supine position with parallel leg position and patella facing upward. The percentage of hip joint migration was recorded. Hip radiographic results were categorized into three groups based on the percentage of hip joint migration: normal (MP 0-32%), subluxation (MP 33-89%), and dislocation (MP ≥ 90 %) (5). The measurement method of MP is demonstrated in Figure 1. The MP value was obtained from medical records. If the MP value was not available in medical records, it was interpreted by a rehabilitation physician or orthopedic specialist with at least 10-years' experience in caring for patients with CP. Despite being a predictor of hip displacement in children with CP (10, 11), the head-shaft angle was not used in this study or in this hospital due to the complexity of the measurement, the variability in its interpretation, and the availability of simpler, standardized alternative measures such as the MP, which is commonly used in medical practice (9, 11).

Statistical analysis

All parameters were described using mean (SD), median (25^{th} percentile, 50^{th} percentile), and frequency (percentage), according to their type and distribution. A probability of less than 5% ($p < 0.05$) was considered statistically significant. All statistical analyses were conducted using STATA version 16 (StataCorp, College Station, Texas, USA). Complete case analysis was used in cases of missing data. No imputation was performed.

Prevalence of hip subluxation/dislocation

The prevalence of hip subluxation/dislocation was calculated as the ratio of the number of participants diagnosed with hip subluxation/dislocation to the number of all participants and is presented as a percentage (1-3).

Development of a prediction model

As this study used a predictive modelling strategy, parameter selection methods were applied to make the final model as parsimonious as possible, i.e., containing a minimal number of predictive parameters. First, data were analyzed using univariable analysis (Fisher's exact test for categorical parameters and the independent t-test for continuous variables) to eliminate all parameters that had $p > 0.2$. After that, univariable and multivariable logistic regression analysis of all remaining parameters was performed to obtain the odds ratio of all parameters. An area under the receiver operating characteristic curve (AuROC) of the regression model was then calculated. The regression model was reduced by removing the least significant factors, then the AuROC was calculated again. The AuROC of the initial model (containing all predictors) and the parsimonious model (containing only statistically significant factors) was compared using the chi-square test. If the AuROC was not significantly different, the model which included less predictive factors were selected as a final model. After that, the regression coefficient of each predictive factor was divided by the smallest one and the results were rounded as an integer to simplify the coefficient. Then, a score from the developed CPR was calculated for all participants.

Evaluation of prediction model performance

The measurement discrimination and calibration were used as a demonstration of clinical prediction score performance (14). To evaluate the model's ability to differentiate between groups (hip subluxation/dislocation and non-hip subluxation/dislocation) was done using the AuROC. The measurement of calibration demonstrated the compatibility between the observed outcomes, represented by a locally weighted scatterplot smoothing (LOWESS) plot, and a predicted probability plot. The LOWESS plot is a regression analysis used to transform raw data into a smooth plot (15). It is an acceptable strategy for evaluating the calibration performance of the CPR (14). A cut-off level for the score was set by applying the diagnostic accuracy test as the level that produced the highest sensitivity and specificity when compared with the true diagnosis of the hip subluxation/dislocation.

Internal validation

According to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline, evaluating internal validation is a requirement for developing CPR. Internal validation was performed using a bootstrapping approach (200 iterations), optimism-corrected C-statistics were used to evaluate model discrimination, and the expected-to-observed ratio was used to assess the model calibration (14).

Sample size calculation

Sample size calculation for the development of prediction model followed the method proposed by Riley, et al. (16). A sample size that had 10 outcome events per predictive factor was used. To keep our CPR from becoming too complicated, we included 3 potential predictive factors and at least 30 outcome events were required.

RESULTS

Characteristics of the participants

During 2018-2023, 131 patients with CP were identified from medical records. Of these patients, fourteen who had incomplete medical data and three who were diagnosed with postnatal CP were excluded from the analysis. Among the 117 initially included patients, 69 had undergone at least one hip radiographic screening, a prevalence of 59%. The data of those 69 patients were included in this study. The mean (SD) age at the time of screening was 113 (242) months (9.5 years) and the median (25th, 75th percentile) were 65 (37, 110). Seventeen patients (25%) were three years old or older at the time of screening. Forty-one patients (59%) were male. Nine patients (13%) were diagnosed as hemiplegic, 28 patients (41%) were diagnosed as diplegic, and 32 patients (46%) were diagnosed as quadriplegic CP. Two (3%), ten (14%), fifteen (22%), eighteen (26%), and twenty-four (35%) patients were categorized as grade 1, 2, 3, 4, and 5, respectively. Forty-two patients (61%) were diagnosed as non-ambulatory, as indicated by a GMFCS grade of 4 or 5. Forty-seven (67%) patients used a universal coverage health insurance scheme, while sixteen patients (23%) and six (9%) patients used cash payment and a health insurance scheme for foreigners, respectively.

Among the 69 patients, 30 were diagnosed with hip dislocation/subluxation, a prevalence of 43%. At the joint level, a total of 129 hip joints were assessed (bilateral for those with diplegia/quadriplegia, unilateral for those with hemiplegia). It was found that 36 joints (28%) had a hip problem. Among the patients with hip subluxation/dislocation (36 hips in 30 patients), it was noted that eight patients had hip dislocation (MP > 90). After orthopedic consultation, all the patients received surgery. Nine patients had MP between 50% and 99%. After orthopedic consultation, four underwent surgery while the remaining five were scheduled for intensive follow-up and received conservative prevention. The remaining patients had MP between 33% to 49% and received conservative prevention after orthopedic consultation (Figure 2).

Compared with the normal hip group, the subluxation/dislocation hip group had significantly more female patients (57% vs 28%, $p = 0.026$; Fisher

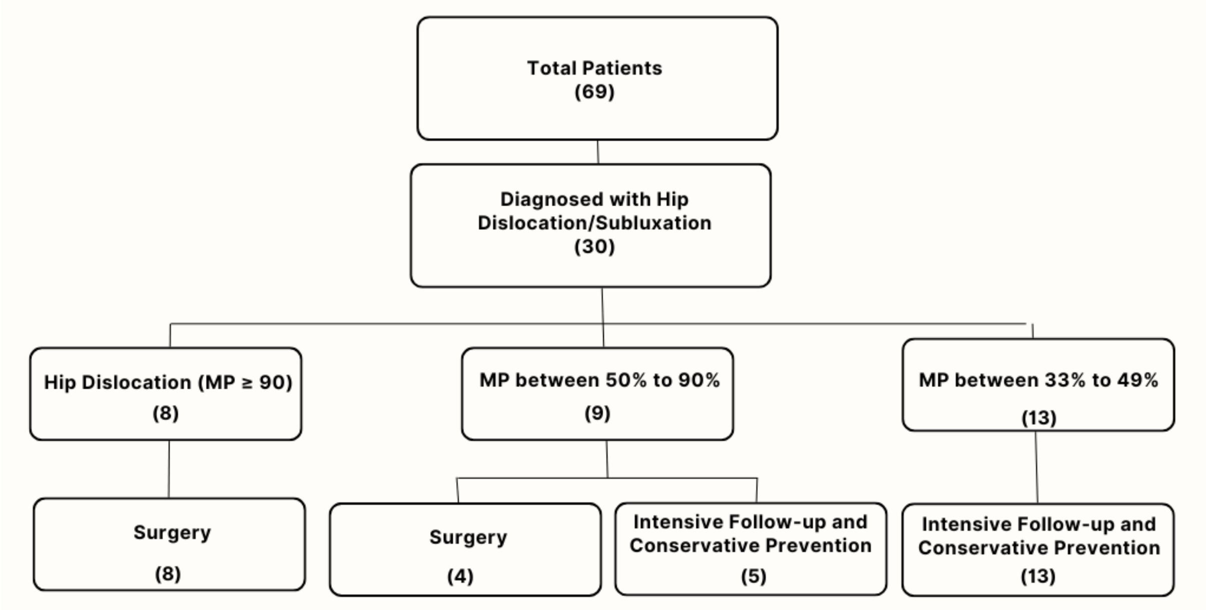

Figure 2. Flow chart of the study and referral/management pathway
MP, migration percentage

Table 1. Characteristics of the participants, categorized by hip subluxation/dislocation status

Parameters	Overall n=69	Hip subluxation/ dislocation n=30	Normal hip n=39	Crude odds ratio (95% CI)#	*p*-value
Age at screening, months					
Mean (SD)	113 (242)	121 (261)	107 (230)	1.00 (0.99-1.01)	0.819
Median (25th, 75th percentile)	65 (37, 110)	69.5 (42, 96)	64 (33, 113)		0.738
Age more than or equal to 3 years, n (%)	17 (25)	12 (31)	5 (17)	1.33 (0.69-7.21)	0.183
Sex, female, n (%)	28 (41)	17 (57)	11 (28)	3.33 (1.22-9.08)	0.026*
Type of CP, n (%)					0.216
Hemiplegic	28 (41)	11 (37)	17 (44)	Reference	
Diplegic	9 (13)	2 (7)	7 (18)	2.26 (0.40-12.97)	
Quadriplegic	32 (46)	17 (56)	15 (38)	3.96 (0.71-22.11)	
GMFCS, n (%)					0.206
Level 1	2 (3)	0 (0)	2 (5)	NA	
Level 2	10 (14)	3 (10)	7 (18)	Reference	
Level 3	15 (22)	4 (13)	11 (28)	0.89 (0.14-4.99)	
Level 4	18 (26)	10 (33)	8 (21)	2.92 (0.57-15.05)	
Level 5	24 (35)	13 (44)	11 (28)	2.76 (0.57-13.29)	
Non-ambulating status (GMFCS 4 and 5), n (%)	42 (61)	23 (77)	19 (49)	3.46 (1.21-9.92)	0.025*
Health insurance scheme					0.471
UC	47 (67)	23 (77)	24 (62)	References	
UC for foreigners	16 (23)	5 (17)	11 (28)	0.52 (0.09-3.13)	
Cash payment	6 (9)	2 (6)	4 (10)	0.47 (0.14-1.58)	

SD, standard deviation; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; UC, Universal Coverage, NA, not applicable
*significant level at $p < 0.05$ by independent t-test for mean (SD), Mann-Whitney U test for median (25th, 75th percentile), and Fisher exact test for n (%); #Crude odds ratio was calculated from univariable logistic regression analysis

exact test) and significantly more non-ambulatory patients (77% vs 49%, $p = 0.025$; Fisher exact test). No significant difference in age, type of CP, or health insurance scheme between the normal and the subluxation/dislocation hip group was found (all $p > 0.05$). Characteristics of this cohort are summarized in Table 1.

Development of CPR

Table 2 demonstrates the results of multivariable logistic regression analyses for diagnostic prediction of hip dislocation/subluxation. The initial model consists of all predictors, including age ≥ 3 years, female sex, non-ambulatory status, type of CP, and health insurance scheme. The AuROC of the initial model was 0.808 (95%CI: 0.704-0.912). The parsimonious model consisted of only the three statistically significant predictors: age ≥ 3 years, female sex, and non-ambulatory status. The AuROC of the parsimonious model was 0.792 (95%CI: 0.684-0.899). Therefore, the parsimonious model was selected as a final model.

A simple CPR was created by dividing the regression coefficient of each factor (8.191 for non-ambulatory status and 5.420 for age ≥ 3 years) by the smallest one (4.549 for female sex) and rounding up, causing a multiplier of one for age ≥ 3 years and female sex and two for non-ambulatory status. A score of the developed CPR was calculated for all patients, resulting in a mean (SD) of 2.20 (1.01). The average score of patients with hip subluxation/dislocation was significantly higher than that of patients with a normal hip (2.93 vs 1.95; $p < 0.001$, independent t-test). The simple CPR is presented in Table 3.

Performance of the developed CPR

Discriminative ability of the developed CPR was evaluated using AuROC of the CPR (Figure 3). The developed CPR had an AuROC of 0.776 (95%CI: 0.668-0.884), indicating an acceptable discriminative ability (10). Calibrating ability of the developed CPR was evaluated using a calibration plot (Figure 4). The calibration plot demonstrates that the predicted probability of developing CPR and the observed probability are the same, i.e., the CPR underestimates the true risk of hip subluxation/dislocation at a score of 0-3 but overestimates the true risk of hip subluxation/dislocation at a score of 4.

Using a cut-off level of scores ≥ 3, the developed CPR has a sensitivity of 73.3% (95%CI: 54.1%-87.7%), a specificity of 76.9% (95%CI: 60.7%-88.9%), a positive predictive value (PPV) of 71.0% (95%CI: 52.0%-85.8%), a negative predictive value (NPV) of 78.9% (95%CI: 62.7%-90.4%), and a positive likelihood ratio (LR) of 3.18 (95%CI: 1.72-5.86). A cut-off level of scores ≥2 has a sensitivity of 93.3% (95%CI: 77.9%-99.2%), a specificity of 35.9% (95%CI: 21.2%-52.8%), a PPV of 52.8% (95%CI:

Table 2. Predictive factors of hip subluxation/dislocation in the initial and final model

Predictive variables	Initial model (AuROC = 0.808 [95%CI: 0.704-0.912])				Final model (AuROC = 0.792 [95%CI: 0.684-0.899])			
	Odds ratio	95%CI of B		*p*-value	Odds ratio	95%CI of B		*p*-value
		Lower	Upper			Lower	Upper	
Age more than or equal to 3 years	7.215	1.257	41.428	0.027*	5.419	1.329	22.099	0.018*
Female sex	6.620	1.775	24.691	0.005*	4.549	1.409	14.687	0.011*
Non-ambulating status	5.571	1.177	26.365	0.030*	8.191	2.214	30.308	0.002*
Type of CP (hemiplegia as a reference)								
Diplegia	4.504	0.542	37.466	0.164				
Quadriplegia	6.106	0.489	76.200	0.160				
Health insurance scheme (universal coverage as a reference)								
Health insurance scheme for foreigners	0.948	0.107	8.429	0.962				
Cash payment	0.294	0.061	1.414	0.127				

B, unstandardized regression coefficient; CP, cerebral palsy
*significant level at $p < 0.05$, multivariable linear regression analysis

Table 3. A simple prediction score for predicting hip subluxation/dislocation

Predictors	Range of test scores	Weighted coefficient	Minimum score	Maximum score
Age more than or equal to 3 years	0-1	1	0	1
Female sex	0-1	1	0	1
Non-ambulating status	0-1	2	0	2
Total score			0	4

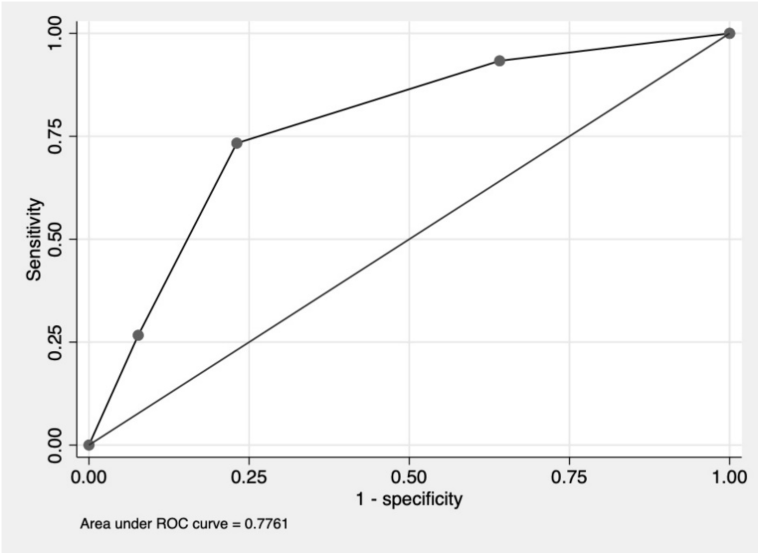

Figure 3. Area under the receiver operating characteristic curve (AuROC) of the prediction score
ROC, receiver operating curve

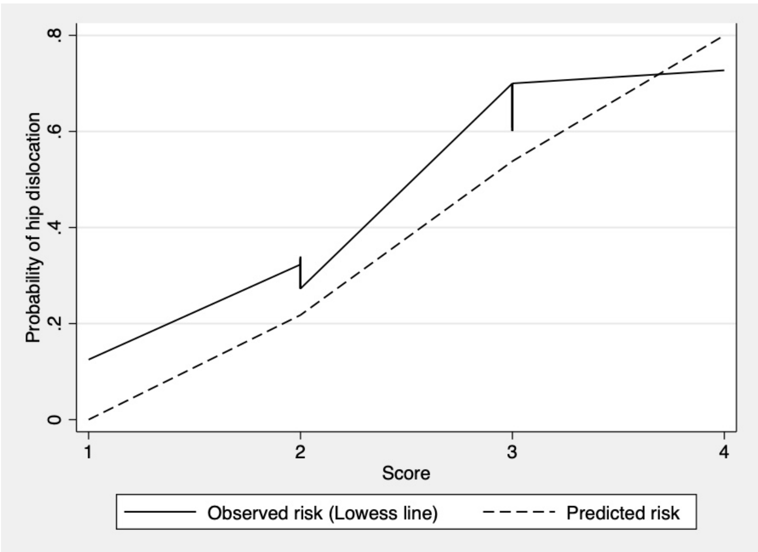

Figure 4. A calibration plot comparing the observed risk to the predicted risk from the prediction score
Lowess, locally weighted scatterplot smoothing

38.6%-66.7%), an NPV of 87.5% (95%CI: 61.7%-98.4%), and a positive LR of 1.46 (95%CI: 1.13-1.88).

Internal validation of the CPR

After applying the bootstrapping approach (200 iterations), optimism-corrected C-statistics were 0.770 (95%CI: 0.676-0.880), and the expected-to-observed ratio of the internal validation model was 1.002 (95%CI: 0.768-1.246), indicating an acceptable internal validation.

DISCUSSION

The prevalence of hip subluxation/dislocation

In this study, the prevalence of hip subluxation/dislocation was 43%, which is comparable to the prevalence reported in high-income countries such as Sweden (2) and Australia (3). However, this prevalence was lower than a previous study from Thailand (4), which reported a prevalence of 57%. This difference might be due to differences in the characteristics of the cohorts. In the present study, only 61% of the participants had GMFCS level IV and V, which indicates a risk for hip subluxation/dislocation, compared with 70% in the previous report (4). Another factor possibly responsible for this difference is the application of a screening program. In Thailand, screening for hip dislocation or dysplasia in CP is not yet widely practiced. The previous study was conducted in the Queen Sirikit National Institute of Child Health which has a screening protocol. However, no hip surveillance protocol was applied in our setting during this study.

Predictive factors of hip subluxation/dislocation

In this study, three predictive factors for hip subluxation/dislocation were proposed, including age ≥ 3 years at screening, female sex, and non-ambulatory status indicated by a GMFCS III of or more. A previous study demonstrated that hip subluxation/dislocation usually occurs at age between two to four years (2). Therefore, participants who were screened at age ≥ 3 years may have a greater risk for developing hip subluxation/dislocation than those who were screened at a younger age. Although no explanatory mechanism was suggested, a previous study reported that female children had a higher risk for hip subluxation/dislocation than male children (8). However, other studies have not demonstrated this association (17). Further studies are needed to confirm the association between female sex and hip dislocation/subluxation. GMFCS is an established risk factor for hip subluxation/dislocation. A comparison among children with CP GMFCS found that those with levels III, IV, and V had a significantly higher relative risks of hip displacement than those with level II (2). However, there have been no studies combining these three risk factors in a single predictive model.

Performance of the prediction score: discriminative ability

The performance of CPR should be evaluated in terms of both discrimination and calibration. Discrimination, i.e., the ability of the CPR to differentiate between patients with and without hip dislocation/subluxation, can be evaluated using the AuROC. The AuROC of this CPR is 0.776 (95%CI: 0.668-0.884), indicating an acceptable discriminative ability (18). This result means that if CPR is used with 100 patients with CP, the hip subluxation/dislocation status of 78 patients would be correctly predicted. On the basis of this AuROC, CPR is appropriate for use as an assistive (used to suggest further investigation to confirm a diagnosis of hip subluxation/dislocation), not as a directive to be used alone for management planning. This discriminative ability could be improved by applying and adjusting the CPR in a larger cohort to ensure an adequate sample size and power of analysis. According to the internal validation of discriminative ability, the C-statistic of 0.770 in the bootstrap model compares well with the 0.776 value in the development model. This result indicates an acceptable increase in the discriminative ability of the CPR (13). It should be noted, however, that this is the first "diagnostic model", i.e., the first developed for predicting a diagnosis of hip subluxation/dislocation at this time point for considering referring to the hospital . Other prediction models are "prognostic models", i.e., prognosing an event in the future, not a condition at the present time (9), thus the performance of the models cannot be directly compared.

Performance of the prediction score: calibrating ability

The calibrating ability of the CPR can be evaluated by assessing the agreement between the predicted probabilities and the observed outcome frequencies in each total score (19). Calibrating ability can be evaluated by various methods, but observing and interpreting a calibration plot is one of the best methods for assessing the calibrating ability of the CPR (19). Although the predicted probability curve and the observed risk LOWESS curve are very similar, the CPR underestimates the true risk of hip subluxation/dislocation at score 0-3 but overestimates the true risk of hip subluxation/dislocation at score 4. Overestimating the risk of hip subluxation/dislocation may not be clinically meaningful; however, the estimation should be taken into consideration if the patient has a score of 0-3 since the observed probability may be higher than the predicted value. As this CPR was developed to be an assistive tool, clinicians should combine the results of the CPR with clinical contexts before judging whether the patient is at risk of hip subluxation/dislocation or not. According to the internal validation of the calibrating ability, the E:O ratio of 1.002 indicates an acceptably overestimated calibrating ability of the CPR (13).

Diagnostic indexes of the CPR

To make the CPR more clinically applicable, a cut-off level has been applied. A cut-off level ≥ 3 has been used because it provides a relatively higher specificity. However, the sensitivity is low, creating a risk of a false negative result (20) and undiagnosed hip subluxation/dislocation. Although a cut-off level ≥ 2 has a relatively lower specificity, its sensitivity is high (93.3%), making it suitable for use as a screening tool. Even using this cut-off point, however, 3% of patients will still miss being referred for investigation (false negative). For that reason, clinicians should use this CPR as an assistive tool for deciding whether the patient should be referred for further investigation to be used together with clinical judgment and an appropriate follow-up strategy, i.e., at least yearly for patients with GMFCS I-II and every six months for patients with GMFCS III-V (4).

Limitations and risks of biases

The main limitation of the study is the small number of patients who were diagnosed with hip subluxation/dislocation. According to the TRIPOD, a minimum of 100 events and 100 non-events should be included to make a predictive model valid (14). In this study, only 30 patients with hip subluxation/dislocation and 39 patients without hip subluxation/dislocation were included. In spite of the low number of patients, the performance of the CPR was acceptable, indicating a possibility for clinical utility. This model should be used as a preliminary CPR and additional external validation studies should be conducted before applying it in actual clinical practice. Another limitation is that we used a retrospective study design, therefore, there was a risk of missing data, a situation which we decided to manage by applying complete case analysis. Additionally, As the recruitment strategy of this study was convenience sampling, it may have affected generalizability of the results as patients with CP who did not come to the hospital for screening may have been at greater risk for hip subluxation/dislocation than those who came to the hospital. Another limitation of this study is that some parameters were not evaluated, e.g., comorbidities as a predictor, as well as femoral head-shaft angle and acetabular index as an outcome assessment measure.

We assessed the risks of bias in this study using the Newcastle-Ottawa Score (NOS) for a cross-sectional study (21). The first component of NOS is selection biases, including representativeness of the sample (non-randomized sampling - 1 point), sample size (not satisfactory - 0 points), non-respondent evaluation (no summary data on non-respondents - 0 points), and ascertainment of the risk factors (hospital records only - 2 points). The second component is the comparability (confounding can be adequately controlled - 1 point). The third component is the outcome, including assessment of outcome (unblinded assessment using objective validated methods - 2 points) and statistical tests (clearly described, appropriate plus measures of association presented including confidence intervals and probability level - 2 points). The total NOS score for this study is 8 points, which is considered a good or low risk-of-bias study.

Clinical and research implications

Since this CPR uses only simple clinical predictors (age, sex, GMFCS), it should be possible to use it in extremely low-resource areas. We plan to use this CPR at outreach clinics where hip radiography cannot be accessed, such in community-level clinics in mountain areas or in temporary clinics near national borders. If the CPR score in a patient with CP is ≥ 3, indicating a high probability of hip subluxation/dislocation, that patient should be referred to a hospital where hip radiography can be used to confirm the diagnosis of hip subluxation/dislocation. However, an external validation study to evaluate predictive performance in that setting should be conducted prior to adopting this CPR in other clinical settings. In the Hip Subluxation Prevention Program for children with CP at Queen Sirikit National Institute of Child Health, it is recommended that treatment should be started in a child with GMFCS level 1-2 who has hip abduction range of motion <45 degrees together with an MP of 30-40% (4). However, in this study, the physical examination data were incomplete and therefore were not used. In future studies, it may be beneficial to include physical examination data in an updated CPR to ensure adherence to the guidelines and potentially improving its performance.

CONCLUSIONS

We introduced our diagnostic CPR for predicting hip subluxation/dislocation in patients with CP from our database including 69 patients with CP and a prevalence of hip subluxation/dislocation of 43%. This CPR may be used to evaluate the risk of hip subluxation/dislocation in settings where hip radiography cannot be accessed. Further external validation studies are needed to confirm the robustness of its performance before applying this CPR in other clinical settings.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

ADDITIONAL INFORMATION

Author contributions

A.K.: was responsible for designing the research question, collecting and analyzing the data, drafting the manuscript and writing the final version of the manuscript; S.P.: was responsible for designing the research question, analyzing the data, and commenting on the final version of the manuscript.

Data archiving

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

Statement of ethics

The authors certify that the protocol of this analysis was approved by the Research Ethics Committee of Nakornping Hospital, Chiang Mai, Thailand, study code:016/67

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Original Article

Open Access

Detection of JunB and C-FLIP Psoriasis Genes Using the Reverse Transcriptase in-situ PCR Technique

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ABSTRACT

OBJECTIVE Psoriasis is a chronic skin disease and considered a multifactorial condition as it is caused by several risk factors; including genetic and environmental interactions. This study aimed to examine localization the expression of *JunB* and *c-FLIP* psoriasis genes at the mRNA cellular level using reverse transcriptase *in-situ* PCR (*in-situ* RT-PCR).

METHODS The *in-situ* RT-PCR technique was used to amplify the targeted mRNA from the formalin-fixed and paraffin-embedded tissues of three psoriasis patients. The localization of *JunB* and *c-FLIP* mRNA expression was achieved using *in-situ* RT-PCR along with the immunodetection technique. An immunohistochemistry profiler was used to count the pixels including the percentage contributions.

RESULTS Hematoxylin and eosin staining revealed the presence of parakeratosis, acanthosis, spongiosis and inflammatory cells. The staining analysis outcomes from *in-situ* RT-PCR and immunohistochemistry detection showed that the *c-FLIP* genes and *JunB* genes were significantly expressed in the surrounding nucleus area at the cellular level of the psoriasis tissue. *JunB* and *c-FLIP* mRNA scored positively in the the immunohistochemical analysis.

CONCLUSIONS RT *in-situ* PCR can be a tool for identifying mRNA cellular gene expression. *JunB* and *c-FLIP* gene expression are significantly present in psoriasis.

KEYWORDS psoriasis, RT *in-situ* PCR, *c-FLIP*, *JunB*

INTRODUCTION

Psoriasis is considered a chronic immune-mediated inflammatory skin disease defined by thickened, flaky skin lesions (1). Psoriasis is thought to be associated with cellular, molecular, and genetic susceptibility to psoriasis (2). Several studies have reported that there is an association between inherited susceptibility genetic variants and environmental risk factors for the development of psoriasis (3). Population based, candidate gene, and genome-wide linkage studies have shown that genetic factors are susceptibility to the development of psoriasis (2).

Numerous studies have identified several psoriasis susceptibility loci, known as psoriasis susceptibility gene 1-9 (PSORS1-9), which contribute to disease susceptibility (4). Among these, PSORS1 is the most strongly associated locus and contains genes such as human leukocyte antigen (HLA)-Cw6, which have been highly correlated with early-onset psoriasis (5). Other important genes include *IL12B* which encodes the p40 subunit of interleukin-12 and interleukin-23 as well as *IL23R*, which plays a crucial role in T-cell differentiation and inflammatory responses (6). Together, these genetic factors underscore the complex and multifactorial nature of psoriasis.

Psoriasis vulgaris is considered to be responsible for growth acceleration, altered variation of keratinocytes, possibly by the activation of cellular immune infiltrates and cytokines (7). The pathological differences affecting the skin in psoriasis are caused mainly by an abnormal skin differentiation secondary to the activation of T-cells or antigen-presenting cells, which triggers various chemokines and cytokines that signal keratinocytes to hyperactive proliferation (8). A study suggested that *JunB* is a component of activator protein-1 (AP-1) transcription factor that is located at the PSORS6 locus and is expressed in healthy human skin could regulate the keratinocyte proliferation and differentiation (9). Epidermal keratinocytes have been shown to reduce the production of *JunB* epithelial cells which activate the cytokine release, attracting neutrophils and macrophages to the epithelium leading to phenotypic improvements in psoriasis were identified (10).

Another study reported that deleting *JunB* and *c-Jun* from epidermal keratinocytes could reproduce can reduce psoriasis. In the patients with psoriasis, the *JunB* gene may be involved in the intricate network of signaling pathways in the immune system which lead to inflammation and skin cell proliferation (11).

Cellular FLICE-like Inhibitory Protein (*c-FLIP*) is a regulatory protein that plays a substantial role in the development of psoriasis, characterized by inflammation and the rapid proliferation of skin cells. A study has shown that the overexpression of *c-FLIP* in certain skin cells could inhibit their programmed cell death and increase the survival of the cells (12).

The *c-FLIP* is a significant antiapoptotic protein that triggers or inactivates signaling proteins for cytoprotection. The *c-FLIP* plays an essential role the development of psoriasis as it is involved in necrosis and autophagy. Compared to the non-lesional skin, the level of *c-FLIP* protein mRNA is higher in lesional skin among psoriasis subjects (13). Studies have reported that the expression of *c-FLIP* and *JunB* genes has a significant multi-functional role in various signaling pathways in psoriasis in animal models (14, 15). Thus *JunB* and *c-FLIP* are considered to be important markers for the level of the susceptibility to posriosis.

In the *in-situ* PCR the targeted gene could be amplified in a fixed cell without distortion of the subcellular components; however, there was a low sensitivity to detecting the gene expression. The reverse transcriptase *in-situ* PCR (RT *in-situ* PCR) method, however, can be used on tissue samples and consists of a combination of reverse transcription of mRNA into cDNA, PCR of cDNA templates with specific primers which can achieve the immunodetection of PCR (16, 17).

In Malaysia, a hospital-based study reported 9.5% of 5,607 dermatological patients were diagnosed with psoriasis; however, the incidence varied with age, gender and ethnicity (18). To the best of our knowledge, there appears to be a lack of studies on genetic factors related to the susceptibility to the development of psoriasis among Malaysians. Detection of *JunB* and *c-FLIP* genes is essential to determining the important mechanisms of keratinocyte proliferation in psoriasis, as they could be genetic markers for psoriasis. Hence, this study was initiated to determine the gene expression of *JunB* and *c-FLIP* using *in-situ* RT-PCR.

METHODS

Ethics statement

The use of archived leftover diagnostic tissues for *in-situ* RT-PCR analysis for research purposes and anonymized patient data analysis has been approved by the ethical committee of the University College of MAIWP International, with the reference (J-160277E). All work has been carried out in compliance with the Helsinki Declaration.

Subjects

Three diagnosed psoriasis subjects were selected based on clinical and histopathological skin biopsy. The psoriasis severity index score was used for assessment of the biopsy site and recorded. The psoriasis severity index scores were high (> 10) in many of the subjects. Diagnoses in the patients were conducted by histopathological examination by identifying the thinning of the suprapapillary plate, intermittent parakeratosis, perivascular infiltration of lymphocytes, and the occasional presence of neutrophil aggregates in the epidermis. Patients with other dermatological conditions such as eczema, allergic contact dermatitis and parapsoriasis were excluded. Figure 1 shows the flow chart of the methodology of this study.

Sample preparation and fixation

Psoriasis vulgaris was diagnosed using the formalin-fixed and paraffin-embedded (FFPE) tissue sections. The FFPE tissue sections were obtained from Lablink (M) Sdn. Bhd. Kuala Lumpur, Malaysia. The morphological changes of the psoriasis tissue were observed using hematoxylin and eosin (H&E) staining. A 50µL of RNase-free DNase I was used to digest the DNA which was then incubated for 20 minutes at 37°C. Diethyl pyrocarbonate water was used to wash the slides, which were rinsed with absolute alcohol for one minute then air-dried and kept for further processing.

One-step RT *in-situ* PCR assay

The Avian Myeloblastosis Virus Reverse Transcriptase (AMV RT) was used to synthesize the first strand of cDNA. The *Tfl* DNA polymerase was used to synthesize the second strand of cDNA and for DNA amplification. The primers were designed using Primer3 and validated and confirmed using the Basic Local Alignment Search Tool (http:/blast.ncbi.nlm.nih.gov/). *c-FLIP* forward: 5'- TGTTGATGCTTTGACTTTC-3', reverse: 5'-AGGGGTCTAC ATGGCAACTG-3' and *JunB* forward primers: 5'-AGAGACAATACAGGCCGCTG -3' and reverse: 5'- TATTTGACCCGCCCAAGC AT-3' were used for *in-situ* RT-PCR.

An incubation chamber was made from *in-situ* coverslips, and the sections were stabilized by an *in-situ* adapter in an Eppendorf Mastercycler (Eppendorf, Hamburg, Germany) along with *in-situ* blocks. The slides were placed in the incubator for the reverse transcription process at 45°C for 45 minutes. The cycling conditions of *in-situ* RT-PCR are as follows: initial denaturation, denaturation, annealing, elongation and final elongation steps were performed for 94°C for 2 minutes, 94°C for 45 seconds, 53°C for 40 seconds, 68°C for 1 minute, and 68°C for 4 minutes for 34 cycles.

Immunodetection of the PCR products

In order to detect the PCR signal, digoxigenin-labelled PCR products were prominent when submerged in 40-µL anti-digoxigenin and diluted in BSA with PBS for 30 minutes at room temperature. The slides were counterstained according to the standard procedure and examined under a light microscope to analyze the images. The specificity of the RT *in-situ* PCR was checked using positive and negative controls. The negative control was digested with DNase and with the exclusion of the reagent primers digoxigenin-11-dUTP and anti-digoxigenin.

Scoring tissue samples

An automated digital application of the immunohistochemistry (IHC) image analysis algorithm was used to assess the staining intensity in tissue sections. The IHC staining intensity of the nuclear-type molecule was evaluated on a scale of "negative (no staining), low positive (< 30% cell staining), positive (30-60% cell staining) and high positive (> 60 % cell staining) (19). The scoring process was automated and used with the ImageJ program based on the macro compatibility that generates a histogram profile of the 3,3′-Diaminobenzidine images.

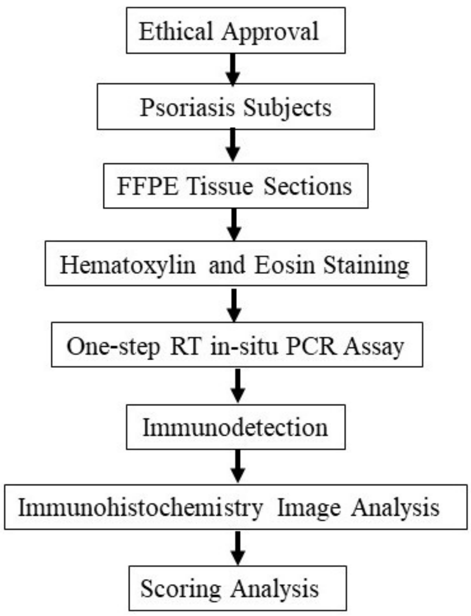

Figure 1. Flowchart of the methodology

RESULTS

Figure 2A shows the acanthosis along the even elongation of the network of the blood vessels in the epidermis. In contrast, the superficial dermis shows an accumulated inflammatory response comprised primarily of small T-lymphocytes (Figure 2B). Spongiosis and parakeratosis are seen in the microphotograph of the hematoxylin and eosin staining of psoriasis tissue section in Figure 2C and Figure 2D, respectively.

The tissue sections treated with proteinase K and DNase I were excluded in the positive control. No signal was detected in the negative control section, while signals in the cells were observed in the positive control but the signals were restricted to the nuclei. This could be due to the exclusion of DNase I in the positive control sections. The cycling conditions and the concentration of the reagents were optimized to detect the *JunB* and *c-FLIP* genes. Figure 3 shows microphotographs of sections through skin tissue affected by psoriasis with the exclusion of digoxigenin-11-dUTP (Fig. 3A), anti-digoxigenin (Figure 3B), primer (Figure 3C) and an intense nuclear signal which was observed in the positive control with the exclusion of DNase I treatment (Figure 3D).

A mild brown color staining was observed in the *c-FLIP* mRNA gene expression (Figure 4A). Using higher magnification, the gene localization was observed clearly. Figure 4B shows the brown signal in nucleus areas (Figure 4B). The IHC analysis showed a positive score with more than 30.00% contribution (36.29%). The *JunB* mRNA was established in all the tissue sections. The gene localization was clearly observed around the nucleus areas, which are marked with an arrow in Figure 4B. The scoring analysis for *JunB* and *c-FLIP* genes is shown in Table 1. There is a higher positive score in *c-FLIP* (24.94%) compared to the *JunB* (36.61%) mRNA. Figure 5 shows the histogram of the scoring analysis for *c-FLIP* mRNA and *JunB* mRNA in tissue samples.

Figure 6A shows the detection of *c-FLIP* mRNA in a psoriasis sample at the higher magnification of 40x. The arrow indicates that the presence of brown color between abundant quantities of nucleus areas. There is a presence of the *c-FLIP* genes in the dermis of the psoriasis tissue section. From the IHC profiler analysis, more than 30.00% were observed in the positive score analysis for *c-FLIP* mRNA in the psoriasis tissue section.

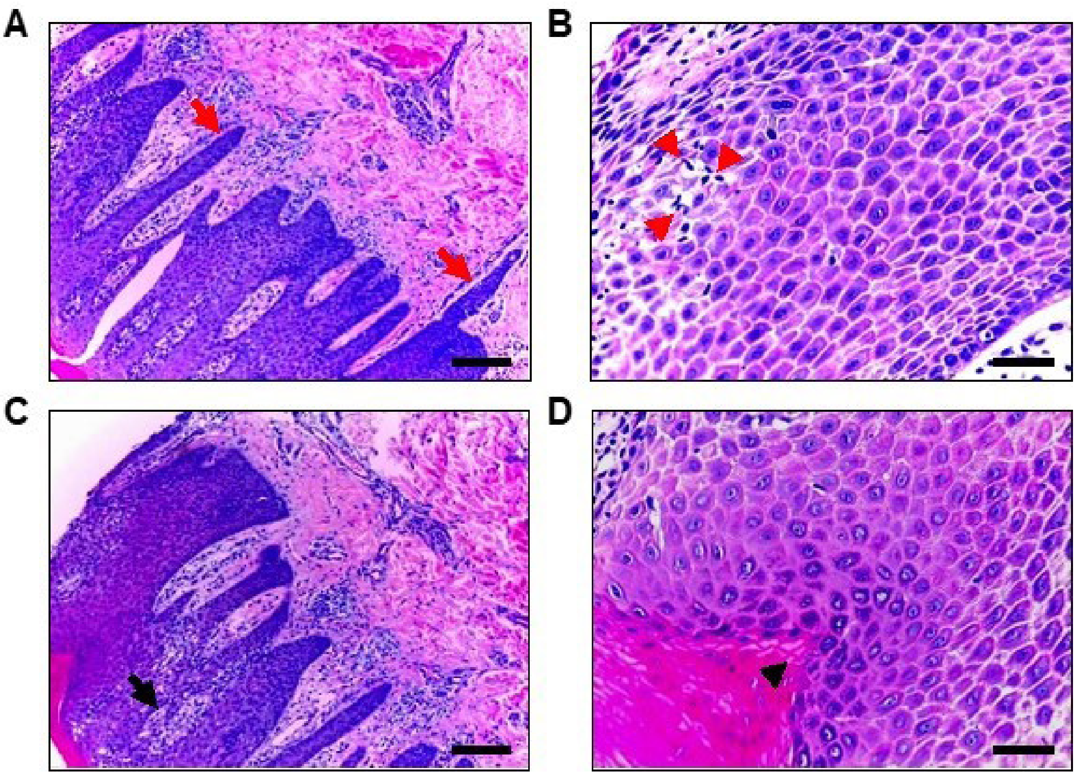

Figure 2. H&E staining of skin sections from psoriasis tissue. (A) acanthosis with irregular hyperplasia (red arrow), (B) infiltration of inflammatory cells (red arrowhead), (C) spongiosis with intraepidermal vesicle (black arrow), (D) parakeratosis with abnormal retention of nuclei (black arrowhead). The scale bars denote 50 μm.

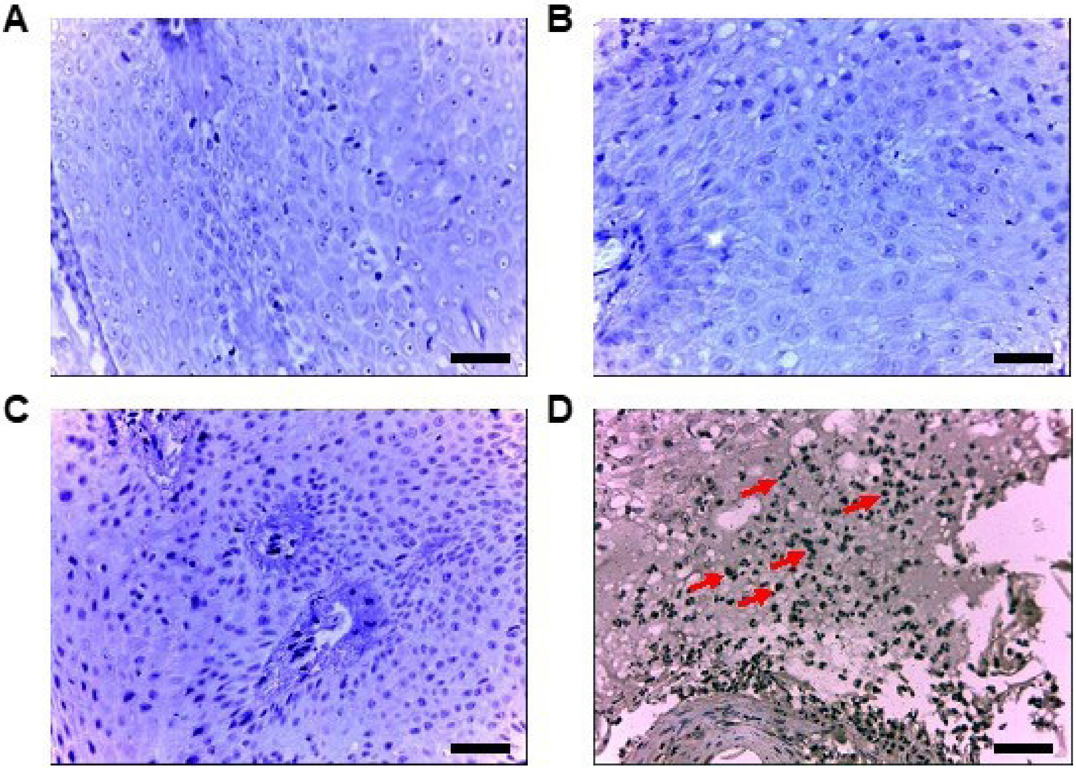

Figure 3. Microphotograph of sections through skin tissue affected by psoriasis. (A) The skin tissue showed the negative control with lack of mRNA signal and the exclusion of digoxigenin-11-dUTP, (B) Skin tissue showed negative control with lack of mRNA signal with the exclusion of anti-digoxigenin, (C) The skin tissue section showed negative control with lack of mRNA signal with the exclusion of primer, (D) The tissue section showed intense nuclear signal (red arrow) in the positive control with the exclusion of DNase I treatment. The scale bars denote 50 μm.

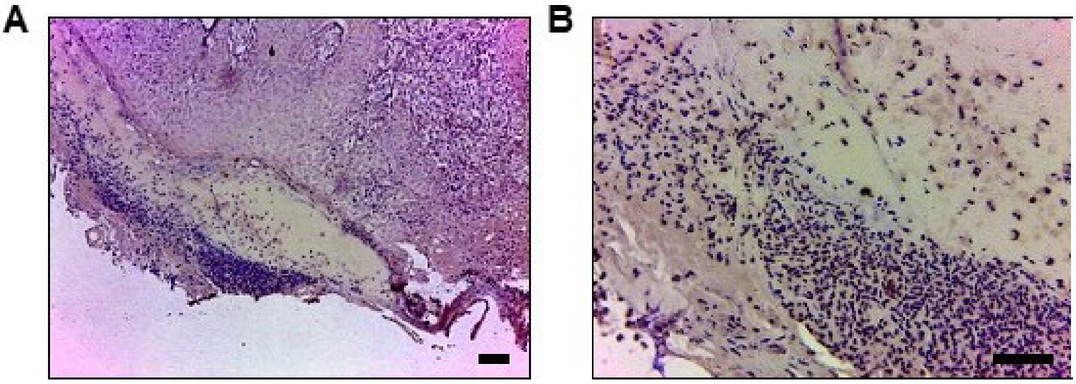

Figure 4. Detection of *c-FLIP* mRNA in psoriatic skin lesion. (A-B) *in-situ* PCR reveals that *c-FLIP* mRNA (brown coloration) is strongly expressed in the nucleus areas of the epidermis. The scale bars denote 50 μm.

Table 1. Scoring analysis for *c-FLIP* mRNA and *JunB* mRNA

Score	Percentage contribution (%)	
	***c-FLIP* mRNA**	***JunB* mRNA**
High positive	24.9492	8.4785
Positive	32.7576	36.2920
Low positive	30.0147	36.6186
Negative	12.2785	18.6110

The *JunB* mRNA shows a positive score in the IHC scoring analysis and shows the presence of the *JunB* gene in the psoriasis tissue sections. Figure 6B shows the presence of brown color at higher magnification.

The observed prominence of the brown color indicates the presence of *JunB* mRNA. This shows that the *JunB* genes play an essential role in the development of psoriasis growth. Depending upon the cell-cycle stage and the external conditions,

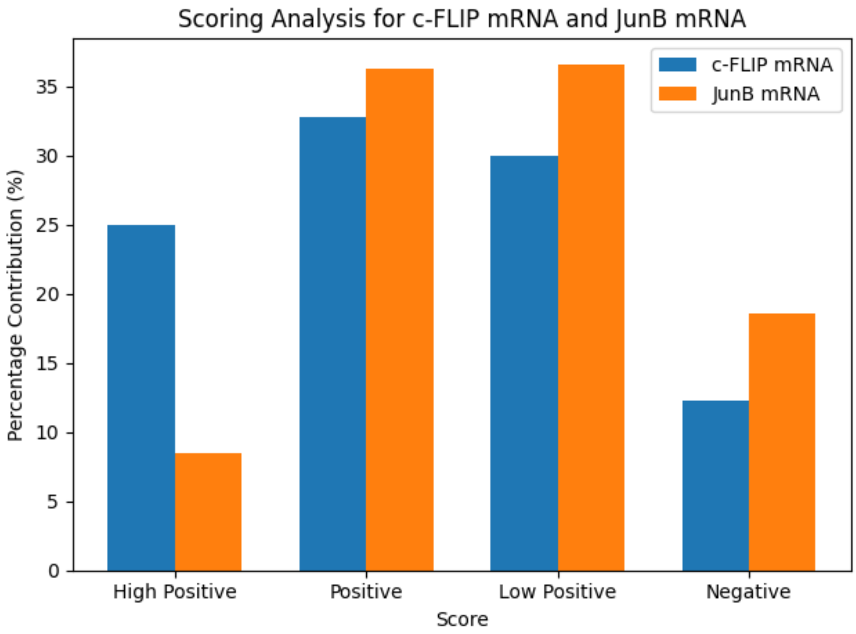

Figure 5. Scoring analysis for *c-FLIP* mRNA and *JunB* mRNA in tissue samples. The bar chart represent the percentage contribution of each score category (high positive, positive, low positive, and negative) for both *c-FLIP* mRNA (blue bars) and *JunB* mRNA (orange bars). The scoring was based automated analysis using ImageJ. The results show variability in the expression levels of both *c-FLIP* mRNA and *JunB* mRNA across different intensity levels, with notable differences in low positive and positive categories.

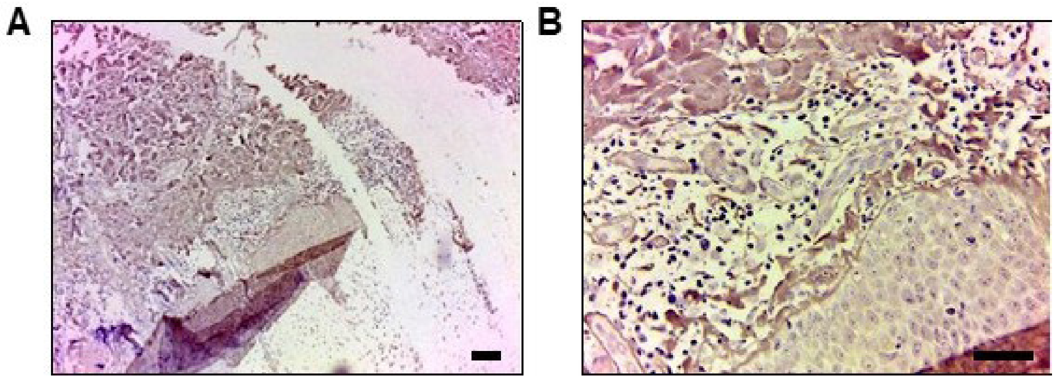

Figure 6. Detection of *JunB* mRNA in psoriatic skin lesion. (A-B) RT *in-situ* PCR technique, the reaction product of *JunB* mRNA (brown coloration) is predominantly located in the nucleus areas of the dermis. The scale bars denote 50 μM

JunB can have either cell division-promoting or preventing activities. *JunB* genes are expressed in the skin tissues that act on keratinocytes to encourage skin proliferation.

DISCUSSION

Expression of *c-FLIP* and *JunB* genes on histological skin sections from psoriasis subjects was determined in this study using *in-situ* RT-PCR. The *in-situ* RT-PCR can be used as a tool for identifying pathological and physiological changes in psoriasis for a specific gene. In light of the results, we strongly conclude that *c-FLIP* and *JunB* genes could be a biomarker for psoriasis, particularly among Malaysians.

Pathogenesis of psoriasis is multifactorial as it involves dysregulated inflammation and genetic predispositions. The cause of psoriasis remains unclear; however, several risk factors play an important role in the development of psoriasis (20). The histology of psoriasis is characterized by parakeratosis, the complex interplay among epidermal keratinocytes, immune cells, inflammatory mediators and hyperplasia (6). Studies have suggested that microRNA (miRNA) could regulate cell-differentiation and proliferation, cytokine responses of keratinocytes, activation and survival of T-cells and the crosstalk between immunocytes and keratinocytes (21). Although the differential expression profile of mRNAs is involved in the development of psoriasis, the biomarkers are not yet used in clinical applications. Studies to determine the role of mRNAs in psoriasis which might lead to prospect insights into diagnosis, pathogenesis and treatment for psoriasis are much needed. For that reason, this study focused on localizing the cellular mRNA of *JunB* and *c-FLIP* gene expression from human psoriasis patients using *in-situ* RT-PCR.

In-situ RT-PCR is considered as a valuable tool for detecting the cell-types in tissue sections (22). The *in-situ* PCR technique was used in this study as it is capable of yielding good results despite low-RNA quantity. The results show that *in-situ* RT-PCR could be considered as a valuable method to detect mRNA expression at the cellular level. *In-situ* RT-PCR combined with immunodetection could be used to determine the localization of *c-FLIP* and *JunB* mRNA expression. The expression of *c-FLIP* and *JunB* genes in the pathogenesis of psoriasis were explored in this study. The *c-FLIP* mRNA showed a positive score using *in-situ* RT-PCR and immunohistochemical methods. The visibility of the brown color indicated the presence of the *c-FLIP* mRNA in our study. This confirms that the *c-FLIP* genes could play a vital role in the development of psoriasis growth (23). The data show that epithelial depletion of *c-FLIP* in keratinocytes could be a necessary step in the drastic death of the cells.

In comparison to RT-qPCR, which offers high sensitivity and precise quantification of gene expression, *in-situ* RT-PCR has the advantage of preserving tissue architecture, thus enabling gene expression detection within specfic skin layers. This is critical for understanding localized diseases like psoriasism where spatial distribution of gene expression, such as *c-FLIP* and *JunB*, is key to predicting disease severity (24), while RT-qPCR lacks spatial information due to tissue homogenization (25). RT *in-situ* PCR was chosen for this study becase it provides valuable insighlts into the localization of gene expression within psoriatic lesions, offering a better understanding of the disease's pathology and its potential role in predicting disease severity (26).

JunB is located in the PSORS6 locus, and the downregulation of *JunB* in the epidermis plays an important role in the pathogenesis of psoriasis (10, 14). All of the psoriasis slide sections showed the presence of the *JunB* gene expression. The histological visualization shows the presence of the *JunB* genes. A study reported that in the tissue extracts of psoriasis lesions expression of *JunB* mRNA was observed. In addition, a gene profiling study noticed increased *JunB* mRNA among Japanese subjects with psoriasis (26). A lack of information on *c-FLIP* and *JunB* protein expression in the epidermis precluded determination of the impact on the severity of the disease.

While the specific mechanisms by which the *JunB* gene contributes to psoriasis are still being elucidated, its involvement highlights the importance of genetic factors in the development and progression of the condition (27, 28). Researchers continue to investigate how alterations in *JunB* expression and function might be targeted for potential therapeutic interventions. Further research is needed to understand the precise mechanism of *JunB* involvement in psoriasis and how it could be leveraged for more effective treatments. Despite significant progress in detecting psoriasis lesions with altered expressions of protein-coding mRNAs, more information from transcriptome studies is needed to understand the cellular processes that are activated in these lesions, including suggesting novel disease mechanisms, biomarkers and possible drug targets. Table 2 shows various studies of psoriasis in different populations using skin biopsies (14, 29-33). A lack of information on *c-FLIP* and *JunB* protein expression in the epidermis precluded determining the impact on the severity of the disease.

This study must be interpreted with consideration of several limitations. Firstly, the sample size is low and outcomes need to be confirmed with larger samples along with control subjects. Secondly, only *c-Flip* and *JunB* genes were focused on, while other activation genes such as HLA, PSOR1 interleukin and antigens in various miRNAs need to be analyzed further. In addition, further assessment is recommended to evaluate the relationship between the gene expression of *c-FLIP*, *JunB* proteins and both the psoriasis area and the severity index score to determine the severity of the psoriasis.

Table 2. Studies of gene expression in skin biopsies in various populations

No	Author, year, reference	Country	Type of study	Samples (psoriasis/controls)	Sample	Gene/protein	Outcomes
1.	Haider et al., 2006 (14)	USA	Observational	26 (26/0)	Skin biopsy	*JunB*	↑*JunB*
2.	Park et al., 2009 (29)	Korea	Case-control	63 (54/9)	Skin biopsy	*JunB*, *c-Jun* and S100A8	↑S100A8 ($p < 0.05$)
3.	Kiafar et al. 2020 (30)	Iran	Observational	20 (20/0)	Skin biopsy	Thioredoxin reductase	↓TrxR ($p < 0.01$)
4.	Dilek et al. 2016 (31)	Turkey	Case-control	75 (50/25)	Skin biopsy	Inducible nitric oxide and myeloperoxidase	↑MPO ($p < 0.05$)
5.	Yldirim et al. 2003 (32)	Turkey	Case-control	44 (22/22)	Skin biopsy	Malondialdehyde	↓MDA skin ($p < 0.01$)
6.	El-komy et al., 2020 (33)	Egypt	Case-control	40 (20/20)	Skin biopsy	miRNA-155, miRNA-210, and miRNA-20b	↑miRNA-155, ↑miRNA-210, and ↑miRNA-20b ($p < 0.05$)
7.	Current Study	Malaysia	Observational	3 (3/0)	Skin biopsy	*c-FLIP* and *JunB*	↑c-FLIP and ↑*JunB*

We suggest that, with the incorporation of the optimization steps, the *in-situ* RT-PCR method could be suitable for visualizing a single cell expressing a specific gene on a tissue section. The mRNA detection is very important to detect the substandard cells at the cellular stage of psoriasis to to facilitate earlier treatment of patients.

CONCLUSIONS

This study clearly demonstrates the presence of *JunB* and *c-FLIP* gene expression using *in-situ* RT-PCR on histological skin sections. *In-situ* RT-PCR shows promise as a valuable method for exploring the relationships between pathological and physiological changes in psoriasis, specifically with respect to gene expression. Further research is needed to validate these findings and explore their correlation with psoriasis severity.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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Original Article

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The Relationship between Hyperuricemia and Anemia in Postmenopausal Korean Women

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ABSTRACT

OBJECTIVE The present study was conducted to assess the association of hyperuricemia and anemia in premenopausal and postmenopausal Korean women.

METHODS Data from 9,239 adults (aged ≥ 20 years) in the Korean National Health and Nutrition Examination Survey VII (2016–2018) were analyzed.

RESULTS After adjustment for related variables (including age), the odds ratio (OR) of hyperuricemia (uric acid [UA] < 6.0 mg/dL), using the normal group (hemoglobin [Hb] ≥ 12.0 g/dL) as a reference, was statistically significantly positively associated with the anemia group (Hb < 12.0 g/dL) in postmenopausal women (OR, 1.615; 95% CI, 1.187–2.198). In premenopausal women, after adjustment for the related variables (except age), the OR of hyperuricemia, with a normal group as a reference, was significantly inversely associated with the anemia group (OR, 0.583; 95% CI, 0.348–0.975). However, with further adjustment for age, hyperuricemia was no longer associated with anemia (OR, 0.679; 95% CI, 0.402–1.148).

CONCLUSIONS Hyperuricemia is positively associated with anemia in postmenopausal women but not in premenopausal women.

KEYWORDS anemia, uric acid, hyperuricemia, women, menopause

INTRODUCTION

Hyperuricemia is characterized by an abnormal increase in serum uric acid (UA) levels (women, UA ≥ 6.0 mg/dL) (1). The prevalence of hyperuricemia varies substantially worldwide, ranging from about 1% to 36% (2). According to data from the US National Health and Nutrition Examination Survey (2015–2016), the incidence of hyperuricemia in US women was 16.4% (20.0 million) (3). An analysis of the Korean National Health and Nutrition Examination Survey (2016) data revealed that the incidence of hyperuricemia in Korean women was 5.9% (4). Hyperuricemia is the most important risk factor for gout, the prevalence of which has risen sharply in recent years in Korea (5). Hyperuricemia is also an important risk factor for chronic kidney disease (CKD) as well as cardiovascular disease (CVD), diabetes mellitus, hypertension, and metabolic syndrome (6, 7).

Anemia is among the most common disorders worldwide. Global estimates indicate that there are approximately 1.62 billion people with anemia, accounting for 24.8% of the overall population (8). Anemia is classified by a reduced hemoglobin (Hb) level (women, Hb < 12 mg/dL) (9). Hyperuricemia and anemia share common comorbidities, such as CKD and CVD (10, 11), and thus may be linked through common pathophysiologic mechanisms.

Hyperuricemia and several other chronic diseases, e.g., hypertension, diabetes mellitus, metabolic syndrome, and CKD, remain areas of active research worldwide. By contrast, investigations into the association of hyperuricemia and anemia are rare. In addition, results can vary according to race, country, and the incidence of the disease. One study argued that UA may protect red blood cells (RBC) due to its antioxidant effect and that it was positively associated with Hb (12). In another study, hyperuricemia was reported to be associated with an increased incidence of anemia in subjects with CKD but not in subjects without CKD (1). Some studies have reported that hyperuricemia is associated with an increased incidence of anemia in subjects with chronic diseases such as metabolic syndrome and hypertension but the incidence of anemia is lower in subjects without these chronic diseases (13, 14). In addition, these results were different for men and women.

Although the causal mechanism linking anemia and hyperuricemia remains unclear, these relationships can differ between premenopausal and postmenopausal women due to menopause-associated changes in sex hormone levels. This study aimed to assess the relationship between anemia and hyperuricemia in Korean women using data from the Seventh Korea National Health and Nutrition Examination Survey (KNHANES VII, 2016-2018).

METHODS

Study subjects

This study was performed using data from the KNHANES VII (2016–2018), Korea Centers for Disease Control and Prevention. KNHANES VII conducted a survey and blood analysis on a total of 24,269 people. The present study limited the analysis to women aged 20 or older among the 9,595 women who participated in KNHANES VII. We excluded 356 individuals with missing data on important analysis variables such as UA, hematocrit (Hct), Hb, and various blood chemistry tests. Finally, 9,239 subjects were included in the statistical analysis. The KNHANES VII study was conducted according to the principles expressed in the Declaration of Helsinki (Institutional Review Board No, 2018-01-03-P-A; 1041479-HR-201804-007). Further information can be found in "The KNHANES VII Sample", which is available on the Korea Centers for Disease Control and Prevention website.

General characteristics and blood chemistry

Research subjects were categorized as either premenopausal or postmenopausal, and lifestyle habits were categorized as regular exercise (yes or no), alcohol drinking (no or yes) and smoking (non-smoker or current smoker). Anthropometric measurements included measurement of diastolic blood pressure (DBP), systolic blood pressure (SBP), waist circumference (WC), and body mass index (BMI). Blood chemistries included measurements of estimated glomerular filtration rate (eGFR), creatinine (Cr), blood urea nitrogen (BUN), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting blood glucose (FBG), white blood cell (WBC), RBC, high sensitivity C reactive protein (hs-CRP), Hb, Hct, platelet (PLT), and UA.

Hyperuricemia and anemia

UA levels were measured by uricase colorimetry (Uric, Eiken, JAPAN) using a Hitachi Automatic Analyzer 7600-210 (Hitachi, Tokyo, Japan). Hyperuricemia was classified as UA ≥ 6.0 mg/dL (15). Hb levels were measured using a SLS Hb detection method (Stromatolyser-FB, 4DL, IM, NR, Sulfolyser, Cellpack, Detergent, Sysmex) using a XN-9000 (Sysmex, Japan). Anemia was defined as Hb < 12 mg/dL (9).

Statistical analysis

The collected data were statistically analyzed using SPSS WIN version 18.0 (SPSS Inc., Chicago, IL, USA). The average and distribution difference in the general characteristics of premenopausal and postmenopausal women were calculated using an independent t-test and chi-squared test (Table 1). The average and distribution difference in clinical characteristics of the normouricemia and hyperuricemia were calculated using an independent t-test and chi-squared test (Table 2). The average and distribution difference in clinical character-

Table 1. General clinical characteristics in women (n (%), mean±SD)

Variables	All women (n = 9,239)	Premenopausal women (n = 4,357)	Postmenopausal women (n = 4,882)	*p*-vlue
Age (years)	51.73±16.53	37.22±9.14	64.74±9.25	<0.001
Current drinker	3,799 (41.1)	2,473 (56.8)	1,326 (27.2)	<0.001
Current smoker	463 (5.0)	287 (6.6)	176 (3.6)	<0.001
Regular exerciser	8,406 (91.0)	3,846 (88.3)	4,560 (93.4)	<0.001
Menstruation	176 (1.3)	176 (4.0)	0(0.0)	<0.001
SBP (mmHg)	117.49±17.78	108.83±12.80	125.23±18.03	<0.001
DBP (mmHg)	73.84±9.62	72.80±9.24	74.76±9.86	<0.001
BMI (kg/m^2)	23.64±3.64	22.87±3.78	24.33±3.37	<0.001
WC (cm)	79.45±9.92	76.01±9.60	82.52±9.16	<0.001
TC (mg/dL)	194.11±37.67	189.79±33.53	197.97±40.63	<0.001
TGs (mg/dL)	117.58±86.24	100.27±74.90	133.03±92.54	<0.001
HDL-C (mg/dL)	54.02±12.70	56.62±12.53	51.70±12.39	<0.001
FBG (mg/dL)	99.16±22.48	93.18±16.10	104.50±25.79	<0.001
BUN (mg/dL)	14.27±4.73	12.19±3.35	16.13±5.01	<0.001
Cr (mg/dL)	0.71±0.22	0.69±0.11	0.73±0.28	<0.001
eGFR (mL/min/1.73 m^2)	97.68±20.70	106.01±18.28	90.25±19.89	<0.001
hs-CRP (mg/L)	1.11±1.88	0.95±1.58	1.26±2.10	<0.001
Hb (mg/dL)	13.12±1.17	12.98±1.25	13.24±1.07	<0.001
Hct (mg/dL)	40.48±3.23	40.25±3.27	40.68±3.19	<0.001
RBC (10^6/μL)	4.37±0.66	4.41±0.39	4.34±0.38	<0.001
WBC (10^3/μL)	5.94±1.64	6.02±1.64	5.86±1.64	<0.001
PLT (Thous/uL)	267.05±64.85	279.13±65.72	256.26±62.12	<0.001
Anemia, n (%)	1,133 (12.3)	657 (15.1)	476 (9.8)	<0.001
UA (mg/dL)	4.45±1.02	4.36±0.93	4.52±1.08	<0.001
Hyperuricemia, n (%)	679 (7.3)	224 (5.1)	455 (9.3)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C reactive protein; Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; WBC, white blood cell; PLT, platelet; anemia, Hb <12.0 g/dL; UA, uric acid; hyperuricemia, UA ≥ 6.0 mg/dL

istics among the non-anemia and anemia participants were calculated using an independent t-test and chi-squared test (Table 3). In the logistic regression for odds ratio of hyperuricemia, the 4 models constructed were: 1) non-adjusted; 2) adjusted for smoking, regular exercising, and drinking or menstruation (premenopausal women only) and models; 3) further adjusted for SBP, hs-CRP, DBP, TC, TGs, BMI, eGFR, WC, FBG, HDL-C, WBC, and PLT; and 4) further adjusted for age (Table 4). The statistical significance level for all data was set as $p < 0.05$.

RESULTS

Clinical characteristics of female research subjects

The clinical characteristics of the research subjects are shown in Table 1. Among the 9,239 subjects, the incidence of anemia and hyperuricemia was 12.3% (premenopausal women, 15.1%; postmenopausal women, 9.8%) and 7.3% (premenopausal women, 5.1%; postmenopausal women, 9.3%), respectively. Compared to premenopausal women, postmenopausal women had higher FBG, hs-CRP, Hb, Hct, BUN, Cr, UA, and a higher incidence of hyperuricemia but lower eGFR, RBC, WBC, PLT, and a lower incidence of anemia.

Clinical characteristics of subjects according to normouricemia and hyperuricemia in premenopausal and postmenopausal women

The clinical features of the study subjects according to normouricemia and hyperuricemia are shown in Table 2. In premenopausal women, FBG, hs-CRP, Hb, Hct, RBC, and WBC were higher in those with hyperuricemia (all, $p < 0.001$), but eGFR ($p < 0.001$), age ($p < 0.001$), and the incidence of anemia was lower compared to those with normouricemia ($p = 0.004$). In postmenopausal women, age, FBG, hs-CRP, WBC, and the incidence of

Table 2. General clinical characteristics according to hyperuricemia status in premenopausal and postmenopausal women

Variables	All women (n = 9,239)		Premenopausal women (n = 4,357)		Postmenopausal women (n = 4,882)	
	Normo-uricemia (n = 8,560)	Hyper-uricemia (n = 679)	Normo-uricemia (n = 4,133)	Hyper-uricemia (n = 224)	Normo-uricemia (n = 4,427)	Hyper-uricemia (n = 455)
UA (mg/dL)	4.27±0.80	6.69±0.75*	4.24±0.78	6.61±0.64*	4.29±0.82	6.73±0.80*
Age (years)	51.32±16.32	57.28±18.18*	37.32±9.11	35.31±9.47*	64.40±9.13	68.09±9.71*
SBP (mmHg)	117.01±17.51	123.54±19.89*	108.50±12.53	114.88±15.96*	124.97±17.76	127.81±20.26*
DBP (mmHg)	73.73±9.41	75.12±11.84*	72.50±8.98	78.37±11.75*	74.89±9.66	73.52±11.57 p = 0.005
BMI (kg/m²)	23.45±3.53	26.08±4.12*	22.68±3.61	26.42±4.96*	24.17±3.30	25.91±3.63*
WC (cm)	78.91±9.69	86.20±10.22*	75.54±9.21	84.63±12.16*	82.06±9.05	86.97±9.03*
TC (mg/dL)	193.80±37.14	198.09±43.62 p = 0.004	188.92±32.71	205.89±43.15*	198.35±40.32	194.25±43.38 p = 0.040
TGs (mg/dL)	114.11±81.29	161.43±125.90*	97.35±70.80	154.19±116.77*	129.75±87.13	164.99±130.14*
HDL-C (mg/dL)	54.42±12.60	48.92±12.80*	56.83±12.47	52.64±13.10*	52.17±12.31	47.09±12.26*
FBG (mg/dL)	98.72±22.51	104.68±21.38*	92.97±16.06	96.96±16.26*	104.09±26.07	108.49±22.55*
BUN (mg/dL)	14.02±4.36	17.42±7.39*	12.13±3.20	13.34±5.38*	15.79±4.54	19.43±7.43*
Cr (mg/dL)	0.70±0.18	0.87±0.43*	0.68±0.09	0.75±0.23*	0.71±0.24	0.93±0.50*
eGFR (ml/min/1.73 m²)	98.94±19.79	81.69±24.51*	106.32±18.12	100.06±20.11*	92.06±18.78	72.64±21.72*
hs-CRP (mg/L)	1.05±1.80	1.83±2.61*	0.90±1.50	1.84±2.53*	1.20±2.02	1.83±2.64*
Hb (mg/dL)	13.11±1.16	13.21±1.33 p = 0.036	12.96±1.26	13.53±1.10*	13.26±1.03	13.05±1.40*
Hct (mg/dL)	40.47±3.18	40.57±3.87 p = 0.451	40.17±3.26	41.67±3.09*	40.75±3.07	40.02±4.10*
RBC (10^6/μL)	4.37±0.35	4.37±0.48 p = 0.813	4.40±0.33	4.55±0.33*	4.34±0.37	4.28±0.49*
WBC (10^3/μL)	5.88±1.62	6.53±1.82*	5.99±1.62	6.66±1.85*	5.80±1.61	6.48±1.79*
PLT (Thous/uL)	266.55±64.35	273.36±70.67 p = 0.008	278.03±65.41	299.32±68.36*	255.82±61.44	260.58±68.32 p = 0.119
Anemia, n (%)	1,030 (12.0)	103 (15.2) p = 0.021	638 (15.4)	19 (8.5) p = 0.004	392 (8.9)	84 (18.5)*

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total Cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C reactive protein; Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; WBC, white blood cell; PLT, Platelet; Anemia, Hb < 12.0 g/dL; UA, uric acid; Hyperuricemia, UA ≥ 6.0 mg/dL; *p-value < 0.001

anemia were higher in those with hyperuricemia (all $p < 0.001$), but eGFR, Hb, Hct, and RBC were lower (all $p < 0.001$) compared to those with normouricemia.

Clinical characteristics of subjects according to non-anemia and anemia in premenopausal and postmenopausal women

Clinical features of the study subjects according to non-anemia and anemia are shown in Table 3. In premenopausal women, age ($p < 0.001$) and PLT ($p < 0.001$) were higher in those with anemia, but BMI ($p = 0.022$), DBP ($p < 0.001$), TC ($p < 0.001$), HDL-C ($p = 0.002$), TGs ($p = 0.001$), Cr ($p = 0.020$), WBC ($p < 0.001$), UA ($p < 0.001$), and the incidence of hyperuricemia ($p = 0.004$) were lower compared to those who were non-anemic. In postmenopausal women, age ($p < 0.001$), SBP ($p = 0.005$), BUN ($p < 0.001$), Cr ($p < 0.001$), hs CRP ($p < 0.001$), UA ($p < 0.001$), and the incidence of hyperuricemia ($p < 0.001$) were higher in those with anemia, but BMI ($p = 0.001$), WC ($p = 0.022$), DBP ($p < 0.001$), TC ($p < 0.001$), HDL-C ($p < 0.001$), TGs ($p = 0.001$), and eGFR ($p < 0.001$) were lower compared to those who were non-anemic.

Comparisons of anemia and hyperuricemia in premenopausal and postmenopausal women

Comparisons of the odds ratio (OR) of hyperuricemia according to anemia status in premenopausal and postmenopausal women are shown in Table 4. After adjustment for related variables

Table 3. General clinical characteristics according to anemia status in premenopausal and postmenopausal women

Variables	All women (n = 9,239)		Premenopausal women (n = 4,357)		Postmenopausal women (n = 4,882)	
	Normo-uricemia (n = 8,560)	Hyper-uricemia (n = 679)	Normo-uricemia (n = 4,133)	Hyper-uricemia (n = 224)	Normo-uricemia (n = 4,427)	Hyper-uricemia (n = 455)
Hb (mg/dL)	13.42±0.81	10.96±1.06*	13.38±0.77	10.78±1.15*	13.45±0.84	11.22±0.86*
Age (years)	51.69±16.45	52.24±17.12 $p = 0.297$	36.78±9.23	39.66±8.19*	64.22±9.09	69.60±9.27*
SBP (mmHg)	117.59±16.45	52.24±17.12 $p = 0.173$	108.77±12.80	109.13±12.81 $p = 0.509$	124.99±17.89	127.43±19.06 $p = 0.005$
DBP (mmHg)	74.23±9.55	70.99±9.63	73.01±9.23	71.60±9.15	75.26±9.69	70.15±10.21
BMI (kg/m^2)	23.72±9.55	23.10±3.37*	22.93±3.85	22.56±3.34* $p = 0.022$	24.38±3.37	23.85±3.37*
WC (cm)	79..65±9.96	77.99±9.47*	76.12±9.71	75.37±8.94 $p = 0.064$	82.62±9.17	81.61±9.00 $p = 0.022$
TC (mg/dL)	195.66±37.77	183.09±35.01 $p = 0.004$	190.92±33.72	183.46±31.71*	199.63±40.44	182.59±39.14*
TGs (mg/dL)	119.57±88.98	103.34±61.48*	101.88±77.52	91.21±57.19*	134.43±95.07	120.08±63.29*
HDL-C (mg/dL)	54.25±12.66	52.35±12.87*	56.87±12.55	55.21±12.35 $p = 0.002$	52.05±12.33	48.40±12.53*
FBG (mg/dL)	99.31±22.29	98.04±23.81 $p = 0.075$	93.27±16.43	92.68±14.07 $p = 0.387$	104.39±25.12	105.45±31.35 $p = 0.394$
BUN (mg/dL)	14.18±4.37	14.93±6.72*	12.20±3.23	12.15±3.98 $p = 0.738$	15.84±4.51	18.78±7.76*
Cr (mg/dL)	0.70±0.16	0.77±0.44*	0.69±0.10	0.68±0.15 $p = 0.020$	0.72±0.20	0.89±0.63*
eGFR (ml/min/1.73 m^2)	97.98±19.93	95.82±25.42*	105.85±18.17	106.84±18.93 $p = 0.201$	91.37±18.91	79.89±25.06*
hs CRP (mg/L)	1.08±1.78	1.31±2.47*	0.94±1.51	1.00±1.94 $p = 0.377$	1.20±1.97	1.74±3.01*
Hct (mg/dL)	41.22±2.52	35.12±2.64*	41.17±2.38	35.08±2.74*	41.27±2.64	35.18±2.51*
RBC (10^6/μL)	4.42±0.32	4.01±0.42*	4.45±0.31	4.18±0.38*	4.40±0.33	3.77±0.35*
WBC (10^3/μL)	5.98±1.63	5.60±1.68*	6.12±1.65	5.49±1.49*	5.87±1.61	5.76±1.91 $p = 0.184$
PLT (Thous/uL)	264.91±62.44	282.36±78.37*	275.50±62.50	299.54±78.52*	256.01±60.90	258.65±71.77 $p = 0.377$
UA (mg/dL)	4.46±0.99	4.38±1.20*	4.41±0.92	4.08±0.97*	4.50±1.04	4.72±1.39*
Hyperuricemia, n (%)	576 (7.1)	103 (9.1) $p = 0.021$	205 (5.5)	19 (2.9) $p = 0.004$	371 (8.4)	84 (17.6)*

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TC, total Cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C reactive protein; Hb, hemoglobin; Hct, hematocrit; RBC, red blood cell; WBC, white blood cell; PLT, Platelet; Anemia, Hb < 12.0 g/dL; UA, uric acid; Hyperuricemia, UA ≥ 6.0 mg/dL; *p-value < 0.001

(including age), the overall OR of hyperuricemia and anemia in women was not significant (OR, 1.208; 95% confidence interval [CI], 0.935–1.560). After adjustment for related variables (except age) in postmenopausal women, the OR of hyperuricemia in the non-anemia group, as a reference, was significant for the anemia group (OR, 1.652; 95% CI, 1.214–2.248). This significance in postmenopausal women (OR, 1.615; 95% CI, 1.187–2.198) remained even with further adjustment for age. In premenopausal women, after adjustment for the related variables (except age), the OR of hyperuricemia in the non-anemia group, as a reference, was significant for the anemia group (OR, 0.583; 95% CI, 0.348–0.975), but the significance disappeared (OR, 0.679; 95% CI, 0.402–1.148) with further adjustment for age.

Table 4. Comparison of anemia and hyperuricemia in premenopausal and postmenopausal women (n = 9,239)

Gender	Category	Hyperuricemia			
		Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)	Model 3 (OR, 95% CI)	Model 4 (OR, 95% CI)
All women (n=9,239)					
Non-anemia	Non-anemia	1	1	1	1
Anemia	Anemia	1.307 (1.050-1.628)	1.310 (1.051-1.633)	1.208 (0.935-1.560)	1.165 (0.899–1.508)
p-value	*p*-value	0.017	0.016	0.148	0.248
Premenopausal women (n=4,357)					
Non-anemia	Non-anemia	1	1	1	1
Anemia	Anemia	0.508 (0.315-0.818)	0.528 (0.327-0.852)	0.583 (0.348-0.975)	0.679 (0.402–1.148)
p-value	*p*-value	0.005	0.009	0.040	0.149
Postmenopausal women (n=4,882)					
Non-anemia	Non-anemia	1	1	1	1
Anemia	Anemia	2.331 (1.800-3.018)	2.389 (1.840-3.102)	1.652 (1.214-2.248)	1.615 (1.187–2.198)
p-value	*p*-value	< 0.001	< 0.001	0.001	0.002

Hyperuricemia, UA ≥ 6.0 mg/dL; non-anemia, Hb ≥ 12.0 mg/dL; anemia, Hb < 12.0 mg/dL
Model 1, Non-adjusted; Model 2, adjusted for smoking, drinking, and regular exercising or menstruation (only premenopausal women); Model 3, Model 2 further adjusted for SBP, DBP, BMI, WC, TC, TGs, HDL-C, FBG, eGFR, hs-CRP, WBC, and PLT; Model 4, Model 3 further adjusted for age

DISCUSSION

The present study investigated the relationship between anemia and hyperuricemia in females using data from the KNHANES VII (2016–2018). Hyperuricemia was positively associated with anemia in postmenopausal Korean women but not in premenopausal women.

Previous studies have revealed that hyperuricemia is closely related to cardiovascular events and worsening of renal function. In a meta-analysis of seven prospective cohort studies and 17 randomized controlled trial studies, the risks of major cardiovascular events (RR 1.35; 95% CI, 1.12–1.62) and adverse cardiovascular events (risk ratio [RR]1.72; 95% CI, 1.28–2.33) were higher in the hyperuricemia group than in the non-hyperuricemia group (16). In a meta-analysis of 13 prospective cohort studies, Li et al. reported that hyperuricemia was an important predictor of the development of newly diagnosed CKD in subjects without CKD (OR, 2.35; 95% CI, 1.59–3.46), and that this association increased with the length of the follow-up period (17). In a study of Chinese adults, Wu et al. reported significantly higher values for BMI, WC, SBP, DBP, FBG, BUN, Crea, TC, TGs, and low-density lipoprotein cholesterol (LDL-C), but lower HDL-C and eGFR (all, $p < 0.001$) for the hyperuricemia group compared to the normouricemia group (18). In our results, hyperuricemia was associated with indices related to CVD and CKD. In the overall population as well as premenopausal and postmenopausal women, the hyperuricemia group had significantly higher BMI, WC, BUN, Cr, SBP, TGs, FBG, and hs-CRP, but lower HDL-C and eGFR compared to the normouricemia group (Table 2). Hyperuricemia adversely affects vascular function by exerting pro-oxidant effects and inducing endothelial dysfunction and inflammation, which may promote CVD (19). Additionally, an increased serum UA level was associated with a decline in renal function and was a strong risk factor associated with initiating dialysis or kidney transplantation (7).

Compared to postmenopausal women, the prevalence of anemia increases in premenopausal women due to menstruation, whereas the incidence of hyperuricemia decreases. In our study, the incidence of hyperuricemia was higher in postmenopausal women (9.3%) than in premenopausal women (5.1%). Previous studies have suggested that the reason for the increase in UA levels in postmenopausal women is a decrease in female hormones due to menopause. In a study of US women, Hak et al. reported that serum UA levels among women with surgical menopause and natural menopause were increased by 0.36 mg/dL (95% CI, 0.14-0.57) and 0.34 mg/dL (95% CI, 0.19-0.49), respectively, compared to premenopausal women (20). They suggested that female hormone use in postmenopausal women can lower serum UA levels (0.24 mg/dL [95% CI, 0.11-0.36]). In a cohort study, Jung et al. reported that the serum UA level increased to 0.87±0.27 mg/dL in the non-hormone therapy group and was significantly higher than the serum UA level in the estrogen and progestogen use therapy group (−0.38±0.29 mg/dL, $p < 0.001$) (21).

The association between anemia and UA is not yet clear. In a cross-sectional study of Chinese adults, Song et al. argued that an increase in UA was associated with an increase in RBC counts (95% CI, 0.003-0.092; B = 0.245, $p < 0.001$) and Hb levels (95% CI, 0.002-0.082; B = 0.138, $p < 0.001$) (12). They suggested that these results were due to the protective role of UA as an antioxidant in RBC. Our results are similar to those of Song et al. In our results for analysis of the overall female population (Table 2), Hb levels in the hyperuricemia group were higher than those in the normouricemia group ($p < 0.001$). However, the results differed between premenopausal and postmenopausal women. Although the RBC counts, Hb levels, and Hct levels were still higher in the hyperuricemia group than in the normouricemia group (all, $p < 0.001$) among premenopausal women, all three variables were lower in the hyperuricemia group than in the normouricemia group among postmenopausal women (all, $p < 0.001$). Some studies have reported that hyperuricemia is positively associated with Hb (22, 23). However, an inverse correlation between Hb concentrations and increasing UA levels has also been reported. One study reported that anemia was positively associated with gout (OR, 1.83; 95% CI, 1.30-2.57), a disease caused by hyperuricemia (24). They argued that anemia is an important risk factor for gout.

There were interesting results in our study. In premenopausal women, the prevalence of anemia in the hyperuricemia group was lower than that in the normouricemia group ($p = 0.004$) but higher than in both the overall female population ($p = 0.021$) and postmenopausal women ($p < 0.001$). In the logistic regression analysis after adjustment for related variables (whether excluding or including age), hyperuricemia in the overall female population was not associated with anemia. However, the results differed when premenopausal and menopausal women were analyzed separately. With further adjustment for age, the inverse correlation between hyperuricemia and anemia was maintained in postmenopausal women (OR, 1.615; 95% CI, 1.187–2.198; $p = 0.004$). In premenopausal women, however, after adjustment for the related variables (except age), hyperuricemia was inversely associated with anemia ($p = 0.040$). This significance disappeared ($p = 0.149$) with further adjustment for age. Increasing age in both men and women is associated with various diseases, such as CKD, diabetes, anemia, and CVD (25). Hyperuricemia can amplify oxidative stress in older individuals and can impinge on diverse physiological systems, thereby accelerating aging and increasing the risk of death (26). In addition, UA accumulation in the elderly is more likely to result in the development of CKD which can then increase the incidence of anemia by reducing the production of erythropoietin (1, 27). In women, the sharp decrease in female hormones due to menopause causes a higher incidence of CVD compared to men (28). In our study, there did not appear to be a distinctive pattern in the relationship between increased age and the incidence of hyperuricemia and anemia in premenopausal women (Figure 1). By contrast, the incidence of hyperuricemia and anemia continued to increase with age in postmenopausal women (Figure 2).

A mechanistic explanation for the differential relationship between anemia and hyperuricemia in premenopausal and postmenopausal women observed in this study cannot be provided at this stage. However, there are potential mechanisms. Hyperuricemia is associated with inflammation. In a cohort study, Spiga et al. reported that hyperuricemia could activate the pro-inflammatory NF-κB signaling cascade, which could lead to the expression of hepatic inflammatory molecules (29). In a cross-sectional study of 2,568 Chinese adults, Zhou et al. reported that hyperuricemia was positively associated with markers of oxidative stress and inflammation such as malondialdehyde, IL-6, and TNF-α (all, $p < 0.001$) (30). Hepcidin, which is involved in iron metabolism, increases during infection and inflammation (31, 32). An increase in the hepcidin level can cause iron dysregulation with hypoferremia and anemia related to inflammatory disease (33). In a cross-sectional study, Bek et al. reported that the

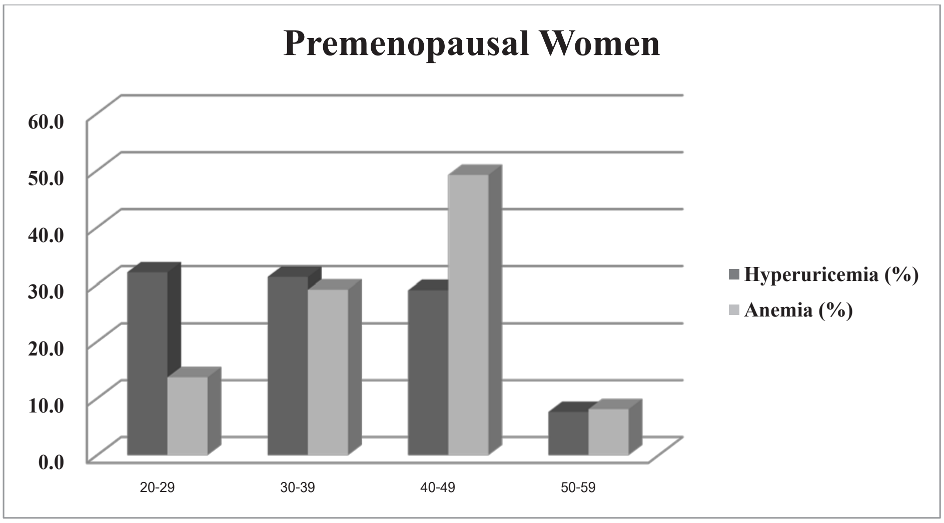

Figure 1. The prevalence of hyperuricemia and anemia by age in premenopausal women
20-29 years (n = 1,000), 30-39 years (n = 1,415), 40-49 years (n = 1,610), 50-59 years (n = 332).

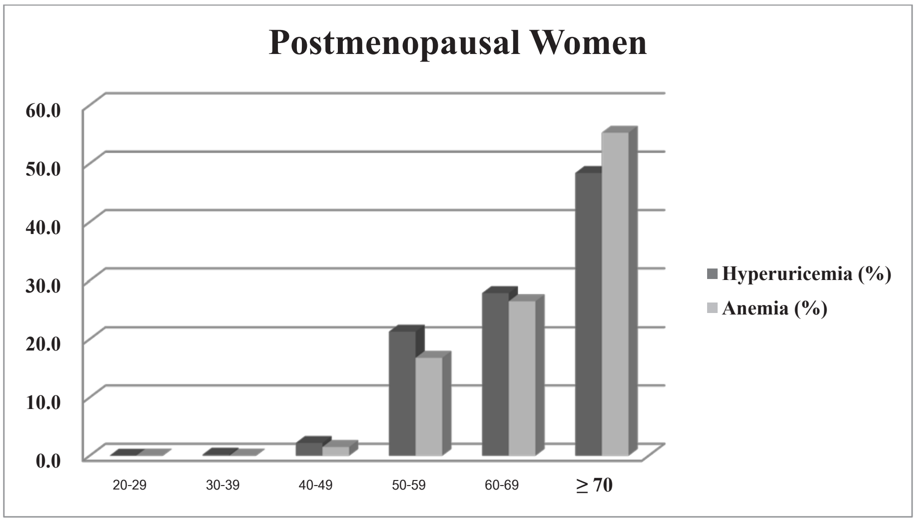

Figure 2. Prevalence of hyperuricemia and anemia by age in postmenopausal women
20-29 years (n=2), 30-39 years (n=6), 40-49 years (n=142), 50-59 years (n=1,505), 60-69 years (n=1,634), 70 years over (n=1,593).

hepcidin level was significantly associated with an elevated serum UA level (r = 0.152, p = 0.002) (34). Compared to premenopausal women, sex hormones in postmenopausal women decrease dramatically with menopause. Female hormones, such as estrogens, are necessary to maintain homeostasis and women's health (35). We believe that the inverse correlation between anemia and hyperuricemia in postmenopausal women is due to the rapid decrease in female hormones, such as estrogens, caused by menopause. The prevalence of hyperuricemia sharply increases after menopause (36). Estrogens play a regulatory role in iron metabolism. They contribute to regulating ferroportin expression through a functional estrogen response element in the promoter of the ferroportin gene (37). In addition, hepcidin inhibition by estradiol (E2) increases intestinal iron absorption and can improve anemia (38).

This study has several limitations. First, parathyroid hormone and serum iron-related indices, such as serum iron, transferrin, ferritin, and iron supplement use, are important in studies related to anemia. In this study, we could not use these variables as an adjustment variable because the KNHANES VII (2016–2018) did not measure serum iron-related indices or record daily iron supplement use. Second, hepcidin plays an important role in the metabolism of serum iron and Hb. But, the KNHANES VII (2016–2018) data did not measure hepcidin levels. Third, the incidence of gout may play an important role in hyperuricemia and anemia. However, the KNHANES VII (2016–2018) data did not examine gout incidence. Thus, parathyroid hormone, iron supplement use, hepcidin, serum iron-related indices, and the incidence of gout should be included as variables of UA and anemia in future studies. Fourth, as a cross-sectional study, the ability to establish a causal relationship between UA and anemia in women is limited. Although this study has limitations, it is the first study to report on the differential relationship between hyperuricemia and anemia in Korean premenopausal and postmenopausal women. More accurate results might be obtained by performing a cohort study.

CONCLUSIONS

The present study investigated the association between hyperuricemia and anemia in Korean women, using data from the KNHANES VII conducted in 2016–2018. Hyperuricemia was positively associated with anemia in postmenopausal women but not in premenopausal women.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest associated with this manuscript.

ADDITIONAL INFORMATION

Authorship confirmation

S.G.K.: conceptualization, formal analysis, writing-original draft, writing-review & editing; M.Y.G.: formal analysis, writing-review & editing; J.A.C.: conceptualization, writing-review & editing; S.Y.P.: conceptualization, writing—review & editing; C.H.P.: writing—review & editing; H.H.S.: conceptualization, formal analysis, writing—review & editing; E.S.H.: conceptualization, writing-review & editing; H.Y.: writing—original draft, supervision writing-review & editing; All authors read and approved the submitted version.

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Original Article

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Validity and Internal Consistency of the Thai Version of a Revised Skin Management Needs Assessment Checklist in People with Spinal Cord Injury: Initial psychometric studies

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ABSTRACT

OBJECTIVE This study aims to cross-culturally translate the revised Skin Management Needs Assessment Checklist (revised SMnac) into Thai (revised SMnac-TH), to evaluate its content validity and internal consistency and to determine the relationship between the revised SMnac-TH score and the occurrence of pressure injuries.

METHODS The study design is a descriptive cross-sectional study. It was conducted at the Inpatient and Outpatient Rehabilitation Medicine Department of Maharaj Nakorn Chiang Mai Hospital, involving one hundred twenty-five Thai people age > 18 years old with spinal cord injury. The French version of the revised SMnac was translated into Thai following the standard guidelines for translation and cross-cultural adaptation. The content validity was evaluated by six experts in rehabilitation medicine. Each of the participants completed the revised SMnac-TH. The internal consistency was measured using Cronbach's alpha coefficient. Logistic regression analysis was used to evaluate the relationship between the revised SMnac-TH score and the occurrence of pressure injuries.

RESULTS The index of item-objective congruence (IOC) of each item ranged from 0.83-1.00. The Cronbach's alpha coefficient of the questionnaire was 0.923. The logistic regression analysis showed no correlation between the revised SMnac-TH score and the occurrence of pressure injuries.

CONCLUSIONS The revised SMnac-TH demonstrated high content validity and internal consistency. It proves to be a useful tool for evaluating pressure injury-related knowledge and skin protective behaviors among Thai individuals with spinal cord injury.

KEYWORDS pressure injury, spinal cord injury, patient education

INTRODUCTION

Pressure injuries represent a significant clinical challenge for individuals with spinal cord injury (SCI) globally (1). The prevalence of pressure injuries among Thai people with SCI is noteworthy. The cross-sectional survey conducted in Chiang Mai in 2003 by Wilekha et al. reported that 80% of 142 individuals with chronic SCI living in the community had experienced a pressure injury at least once (2). A 2015 cross-sectional study by Kovindha et al. in Chiang Mai, found that 26.4% of 129 Thai individuals with chronic SCI who used wheelchairs had pressure injuries at the time of the study (3). Similarly, in a recent study by Poolpipat et al. conducted in Nakhon Ratchasima, a prevalence of pressure injuries of 29.3% was reported (4). Pressure injuries can lead to deteriorating health conditions, ultimately impacting quality of life and independence (5).

In addition to motor and sensory impairments, individuals with SCI are prone to several conditions that increase the risk of pressure injuries, e.g., prolonged immobility, malnutrition, autonomic dysreflexia, spasticity, incontinence, sarcopenia and skin changes (6, 7). The study by Poolpipat et al. which examined factors associated with pressure injuries in Thai individuals with SCI who use a wheelchair independently found that friction and shear forces from improper transferring and prolonged sitting are significant factors that increase the risk of pressure injuries (4). The study by Silva et al. on the risk factors for pressure injuries in adults with SCI undergoing neurological rehabilitation reported that while some risk factors are non-modifiable, e.g., advanced age, longer time since injury, and a complete lesion, are also modifiable risk factors. For example, smokers are three times more likely to develop pressure injuries compared to non-smokers. Additionally, nonadherence to preventive behaviors, such as pressure relief actions and prolonged wheelchair sitting, increases the risk of developing pressure injuries (8). The self-management and prevention strategies for pressure injuries in people with SCI primarily focus on avoiding or redistributing mechanical factors such as pressure, shear, and friction, using appropriate support surfaces such as seat cushions and mattresses, managing modifiable risk factors, maintaining proper nutrition, and adopting skin protective behaviors (9). These skin management and prevention strategies are integrated into patient education and training during rehabilitation programs.

The Spinal cord injury Research Evidence (SCIRE) Professional, which compiles current SCI evidence and resources, provides tools for assessing pressure injuries. Most of these tools are designed to assess the risk of pressure injury development, such as the Braden Scale, Spinal Cord Injury Pressure Ulcer Scale (SCIPUS) and the Waterlow Pressure Ulcer Scale (10). The Skin Management Needs Assessment Checklist (SMnac), derived from the Needs Assessment Checklist, was developed in 2004 by Paul Kennedy and colleagues (11). It has been reviewed as the only tool specifically for assessing knowledge and ability to perform skin checks, pressure relief, and prevention of skin breakdown (10). The SMnac has demonstrated high internal consistency and sensitivity to change (11).

In 2011, Anthony Gélis and colleagues translated and adapted the SMnac into French, resulting in a revised version (12). This self-administered questionnaire is comprised of a total of 20 questions, with the first question asking whether the individual has a mirror for skin inspection. The remaining 19 questions are divided into three domains: skin checks (4 items), preventing pressure injuries (11 items), and preventing wounds (4 items). Each item is scored from 0 to 3 (0 = completely dependent, never does; 3 = completely independent, always does or instructs someone to do). The total score is expressed as a percentage, with a higher score indicating better knowledge of pressure injuries and better adherence to skin protective behaviors. The revised SMnac has exhibited good internal consistency, validity, and reliability, making it a valuable tool for assessing knowledge and skin protective behaviors after individuals with SCI have been educated on skin management to prevent pressure injuries (9, 12). The revised SMnac has recently been translated into a Malay version (13), but no Thai translation of the revised SMnac has been reported.

The aims of this study are to translate and cross-culturally adapt the French version of the revised SMnac into the Thai language, to evaluate its content validity and internal consistency, and to determine the relationship between revised SMnac-TH scores and the occurrence of pressure injuries.

METHODS

This study protocol was approved by the institutional Ethics Committee of the Faculty of Medicine, Chiang Mai University, study code: REH-2564-08267.

Participants

The sample size was calculated using the Bonett method to assess internal consistency using Microsoft Excel, resulting in 125 subjects

(14). One hundred twenty-five Thai inpatients and outpatients with traumatic or non-traumatic SCI who visited Department of Rehabilitation Medicine at Maharaj Nakorn Chiang Mai Hospital between August 2021 and October 2022 were recruited. The inclusion criteria included age 18 or older, proficiency in the Thai language and the ability to read independently. Individuals with severe cognitive impairment or severe mental disorders were excluded.

Development of the revised SMnac-TH

Translation and cross-cultural adaptation process

Permission for translation was granted by Dr. Anthony Gélis via electronic mail. The translation process was conducted in accordance with the guidelines proposed by Beaton et al. (15).

Forward translation: The French version of the revised SMnac was independently translated into two draft versions of the revised SMnac-TH by two linguistic experts from the Humanities Academic Service Center, Chiang Mai University. Subsequently, the authors analyzed the items in each draft version and synthesized them into a single draft version of revised SMnac-TH.

Backward translation: Two back-translations were independently conducted by two native French speakers who were proficient in the Thai language. Neither of the translators were health professionals and they were unaware of the original version of the revised SMnac. These versions were sent to Dr. Anthony Gélis for review and feedback. After receiving feedback and suggestions, the initial draft of the SMnac-TH was modified into the prefinal version of the revised SMnac-TH.

Evaluation of content validity of the revised SMnac-TH

The pre-final version of the revised SMnac-TH was tested for content validity by six experts in rehabilitation medicine. Each expert rated each of the items on a scale of +1 for clearly measuring the objective, -1 for clearly not measuring the objective, or 0 for an unclear degree of congruence with the content area (16). The index of item-objective congruence (IOC) was calculated by dividing the total score for each item by 6. An IOC value of 0.7 or higher was considered acceptable (17).

Pilot study

Twenty Thai individuals with SCI completed the pre-final version of the revised SMnac-TH to identify any confusion or misunderstandings (18). Subsequently, adjustments were made to simplify the questionnaire's usage and to enhance understanding. The final versions of the SMnac-TH, in both Thai and English, are provided in the Supplementary appendix.

Data collection

After providing written informed consent, participants completed the revised SMnac-TH. If they encountered difficulties with writing, they were allowed to receive assistance. Demographic data, lesion characteristics, and information regarding pressure injuries were collected from medical records and interviews. The data were recorded using the International SCI Core Data Set version 3.0 (19).

Statistical analysis

All statistical analyses were preformed using SPSS version 22.0. Descriptive statistics were used to report the characteristics of the study population. Frequency and percentage were used to describe categorical variables, mean and standard deviation (SD) for normally distributed numerical variables, and median with interquartile range (IQR) for non-normally distributed numerical variables.

The IOC was used to evaluate the content validity of the questionnaire. An acceptable IOC value for each item was 0.7 or greater (17). The internal consistency was assessed using Cronbach's alpha coefficients. Values of 0.7 or higher were considered adequate (20). Logistic regression analysis was performed to assess the relationship between the revised SMnac-TH score and the occurrence of pressure injuries. This involved categorizing participants into one of two groups: those with pressure injury or history of pressure injury within the past 12 months, and those without any history of pressure injury. The odds ratio was determined using the Wald test. Odds ratios close to 1 or exactly 1 and a p-value greater than 0.05 suggested that the score was not statistically significantly related to the occurrence of pressure injuries.

RESULTS

Characteristic of the study population

One hundred twenty-five individuals with traumatic or non-traumatic SCI were enrolled. Most participants were male (86/ 125, 68.8%).

The majority were paraplegia with ASIA (American Spinal Injury Association) Impairment Scale (AIS) group A, B, or C (76/125, 60.8%). Eighteen participants (14.4%) had pressure injury at the time of the study, and 22 (17.6%) participants had had pressure injury within the past 12 months. The characteristics of the study population are presented in Table 1.

Table 1. Characteristics of the study population

Sociodemographic	n (%)
Gender	
Male	86 (68.8)
Female	39 (31.2)
Age group	
18-29 years	15 (12.0)
30-59 years	81 (64.8)
> 60 years	29 (23.2)
Education level	
Primary school or below	41 (32.8)
Secondary school	59 (47.2)
College or above	25 (20.0)
Lesion characteristics	
Time since injury (years)	
< 1	24 (19.2)
1–4	23 (18.4)
5–9	21 (16.8)
10–14	19 (15.2)
≥ 15	38 (30.4)
Etiology of SCI	
Traumatic	106 (84.8)
Non-traumatic	19 (15.2)
Severity of SCI	
C1–4 AIS A, B and C	4 (3.2)
C5–8 AIS A, B and C	26 (20.8)
T1–S3 AIS A, B, and C	76 (60.8)
AIS D at any NLI	19 (15.2)
Lesion	
Complete SCI	72 (57.6)
Incomplete SCI	53 (42.4)
Pressure injury	
Absence of pressure injury	107 (85.6)
Presence of pressure injury	18 (14.4)
History of pressure injury in the past 12 months	22 (17.6)
Absence of pressure injury	14 (63.6)
Presence of pressure injury	8 (36.4)
Site	
Sacral	11 (61.1)
Ischial tuberosity	5 (27.7)
Heel	1 (5.6)
Trochanter	1 (5.6)

SCI, spinal cord injury; ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale, NLI, neurological level of injury

Translation and cross-cultural adaptation into the revised SMnac-TH

The draft version of the revised SMnac-TH underwent three revisions, finally resulting in IOC values of 0.83-1.00 for each item, indicating acceptable content validity of the questionnaire. The IOC for each item is shown in Table 2. In the pilot study, participants reported that the revised SMnac-TH version was easy to understand for most items. However, there were some areas of confusion due to translation and cultural differences. Adjustments were made by altering the words used and subdividing items 3, 12, and 15 into two sub-items to simplify the revised SMnac-TH.

The revised SMnac-TH

The revised SMnac-TH comprised 20 main items, with items 3, 12, and 15 each containing 2 sub-items, resulting in a total of 23 items. Item 1 inquired whether the individual had a mirror for skin inspection, while the remaining 22 items were distributed across three domains:

1. Skin Checks (5 items, 15 points)
2. Preventing Pressure Injuries (13 items, 36 points)
3. Preventing Wounds (4 items, 12 points)

The total score ranged from 0 to 63, with a higher score indicating better knowledge of and skin management behaviors for preventing pressure injuries.

Psychometric properties of the revised SMnac-TH

In terms of internal consistency assessment, it was found that the Cronbach's alpha value was 0.923. For the logistic regression analysis, the participants were divided into two groups: those with pressure injury or a history of pressure injury within the past 12 months, and those without any history of pressure injury. A higher score on the revised SMnac-TH indicated a greater knowledge of pressure injury prevention and adherence to skin management behaviors. The study had an odds ratio of 0.99 (p = 0.80), suggesting that the scores were not significantly associated with the occurrence of pressure injuries. Additionally, there was no statistically significant difference in mean scores between the two groups of participants (p = 0.799) as shown in Table 3.

Table 2. Index of item-objective congruence (IOC)

Item number	First time	Second time	Third time
1	0.67	0.67	0.83
2	0.67	1.00	-
3	0.50	0.83	-
4	0.67	0.67	0.83
5	0.50	1.00	-
6	1.00	-	-
7	1.00	-	-
8	0.83	-	-
9	1.00	-	-
10	1.00	-	-
11	1.00	-	-
12	0.83	-	-
13	1.00	-	-
14	1.00	-	-
15	0.83	-	-
16	0.83	-	-
17	0.83	-	-
18	0.83	-	-
19	0.83	-	-
20	0.83	-	-

DISCUSSION

In the process of translation and cross-cultural adaptation, discrepancies were identified between the forward-translated and backward- translated versions. Most of the disparities were found to be in translations where linguistic experts adhered to the literal meaning of the words that did not convey the medical meanings. The language was adjusted to ensure appropriateness and accuracy in medical contexts, e.g., substituting the word "รูเปิด" (open hole) with "แผลเปิด" (open wound). the authors further adapted the questionnaire by adding sub-items to items 3, 12, and 15. The details and rationale for these modifications are presented in Table 4.

This study examined the content validity and internal consistency of the revised SMnac-TH questionnaire. Results revealed that each question demonstrated an IOC value of greater than 0.7, indicating good content validity. Additionally, Cronbach's alpha coefficient had a value of 0.923, which exceeds 0.7, suggesting high reliability in terms of the internal consistency of the questionnaire. This finding is comparable to the study of the French version of revised SMnac by Anthony Gélis, et al. which found a Cronbach's alpha coefficient of 0.907 (9) and the study of the Malay version of the revised SMnac which showed a Cronbach's alpha coefficient of 0.994 (13). Thus, it can be inferred that the revised SMnac questionnaire in both Thai and other languages demonstrated a high level of reliability.

The logistic regression analysis found that the total scores of the questionnaire were not associated with the occurrence of pressure injuries. Therefore, the total scores of the questionnaire cannot predict whether pressure injury will occur or not. This aligns with the study by Groah et al. which evaluated factors affecting pressure injury occurrence in spinal cord injury individuals and found that pressure injury occurrence was related to various factors, not solely based on knowledge of or adherence to skin management behaviors (21). Similarly, studies in Thailand found that prior knowledge about pressure injuries did not exhibit a statistically significant correlation with the presence or absence of pressure injuries (2, 4). However, patient education was shown to have a significant impact on skin management ability (7). High total scores of the revised SMnac indicates that individuals have knowledge of and adhere to pressure injury prevention protocols. Therefore, the revised SMnac is suitable for assessing an individual's knowledge of and adherence to preventive behaviors after receiving education about pressure injuries or before discharge from

Table 3. Average total scores between the group with pressure injury or a history of having pressure injury in the past twelve months and the group without pressure injury

	Group with pressure injury or a history of pressure injury (n)	Group without pressure injury (n)	*p*-value
Total Scores (mean ± 2SD)	33.53±12.994 (32)	34.23±13.376 (93)	0.799^t

^{t}, student t-test; SD, standard deviation

Table 4. Item adaptations and rationale

The French version revised SMnac	The Thai version revised SMnac	Rationale for adaptation
3. *Savez-vous quoi rechercher et où regarder?* (3. Do you know what to look for and where to look?)	3.1 ท่านรู้หรือไม่ว่าต้องดูผิวหนังบริเวณไหน (3.1 Do you know which areas of the skin to examine?) 3.2 ท่านรู้หรือไม่ว่าต้องมองหาความผิดปกติอะไร (3.2 Do you know what abnormalities to look for?)	The French version consisted of two questions in one item, which might cause confusion and lead to erroneous responses. Therefore, the authors divided these items into two sub-items (3.1, 3.2) to make it more convenient for individuals to choose their answers.
12. *Savez vous contrôler la qualité de gonflage de votre coussin?* (12. Do you know how to check the condition of your seat cushion?)	12.1 ท่านใช้เบาะรองนั่ง (เบาะลม เบาะโฟม หรือเบาะชนิดอื่น) หรือไม่ (12.1 Do you use a seat cushion (air cushion, foam cushion, or other types)?) 12.2 ท่านรู้วิธีตรวจสอบสภาพเบาะรองนั่งหรือไม่ (12.2 Do you know how to check the condition of the seat cushion?)	The authors added a sub-item to item 12 regarding the use of seat cushions, asking whether the respondent had used a seat cushion or not, without scoring the sub-item 12.1. If a seat cushion had been used, then the respondent proceeded to the next sub-item (12.2) which asked whether the individual knew how to check the cushion. In cases where the individual had not used a seat cushion, they might not be aware of how to assess its condition. The score for sub-item 12.2 for individuals without a seat cushion would be 0.
15. *Positionnez vous vos oreillers correctement dans votre lit (seul ou avec l'aide d'un tiers*)?* (15. Do you position your pillows correctly in your bed (by yourself or with assistance*)?)	15.1 ท่านรู้วิธีจัดท่านอนบนเตียงโดยใช้หมอนวางตำแหน่งที่ถูกต้องเพื่อป้องกันแผลกดทับหรือไม่ (15.1 Do you know how to position yourself in bed using pillows correctly to prevent pressure injuries?) 15.2 ท่านได้จัดท่านอนดังข้อ 15.1 หรือไม่ (ทำเองหรือมีคนช่วย*) (15.2 Have you positioned yourself in bed as described in item 15.1 (by yourself or with assistance*)?)	The original version consisted of two questions in one item, which might cause confusion and lead to erroneous responses. Therefore, the authors divided these items into two sub-items (15.1, 15.2) to make it more convenient for individuals to choose their answers.

Revised SMnac, Revised Skin Management Needs Assessement Checklist

the hospital to review understanding and can also be used for long-term assessment of individuals with SCI.

Limitations

Limitations of this study include that, in the questionnaire when respondents were asked whether they knew something or not, their responses were not verified by medical personnel regarding the accuracy of their knowledge. Therefore, it would be beneficial if individuals could provide clearer and more detailed descriptions in their answers. Furthermore, this study did not assess the test-retest reliability due to time limitations in scheduling repeat questionnaire completions with the participants because of time constraints imposed by the COVID-19 situation. In the future, it may be necessary to assess reliability through test-retest methods and it may also be necessary study the responsiveness of the revised SMnac-TH questionnaire. Additionally, it may be useful to investigate the relationship between various factors of spinal cord injured individuals that could potentially affect the scores of the revised SMnac-TH for use in planning, education and monitoring of skin management and pressure injury prevention in each spinal cord injured individual appropriately.

CONCLUSIONS

The Thai version of revised Skin Management Needs Assessment Checklist (SMnac-TH) has high content validity and internal consistency. It is a useful tool for assessing pressure injury related knowledge and skin protective behaviors among Thai people with spinal cord injury.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ADDITIONAL INFORMATION

Author contributions

C.S., P.P., and S.T.: designed the research questions and methodology; C.S. and P.P.: collected the data; C.S., P.P., and S.T.: analyzed the data and drafted the manuscript; C.S.: wrote the final version of the manuscript; S.T.: provided feedback on the final version.

Supplementary materials

The following supporting information can be downloaded at: Supplementary appendix

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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แบบสอบถามเกี่ยวกับการดูแลผิวหนังของผู้ป่วยบาดเจ็บไขสันหลังฉบับปรับปรุง ฉบับภาษาไทย

โปรดทำเครื่องหมาย ✔ ตามความเห็นของท่าน

การดูแลผิวหนัง

1 **ท่านมีกระจกเงาบานเล็กสำหรับสำรวจผิวหนังหรือไม่** ☐ ไม่มี ☐ มี

การตรวจสอบสภาพผิวหนัง

2 **ท่านรู้วิธีสำรวจผิวหนังของท่านโดยใช้กระจกเงาหรือไม่**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

3.1 **ท่านรู้หรือไม่ว่าต้องดูผิวหนังบริเวณไหน**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

3.2 **ท่านรู้หรือไม่ว่าต้องมองหาความผิดปกติอะไร**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

4 **ท่านรู้วิธีคลำผิวหนังเพื่อตรวจหาแผลกดทับชนิดที่ไม่เป็นแผลเปิดหรือไม่**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

5 **ท่านตรวจสอบสภาพผิวหนัง ตามที่ได้สอนดังข้อ 2, 3.1, 3.2 และ 4 หรือไม่ (ทำเองหรือมีคนช่วย*)**

☐ 0: ไม่เคยทำ ☐ 1: ทำบางครั้ง ☐ 2: ทำบ่อยครั้ง ☐ 3: ทำเป็นประจำ

การป้องกันการเกิดแผลกดทับ

6 **ท่านรู้วิธีการลดแรงกดทับ เช่น การยกตัว หรือ ก้มตัวไปข้างหน้า หรือไม่**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

7 **ท่านรู้หรือไม่ว่าควรลดแรงกดทับบ่อยเพียงใดและแต่ละครั้งใช้เวลานานเท่าไร**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

8	**ท่านรู้หรือไม่ว่าการสูบบุหรี่จะเพิ่มความเสี่ยงต่อการเกิดแผลกดทับและทำให้แผลหายช้า**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
9	**ท่านรู้หรือไม่ว่าการนั่งบนเก้าอี้นานเกินไปจะเพิ่มความเสี่ยงต่อการเกิดแผลกดทับ**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
10	**ท่านรู้หรือไม่ว่าการรับประทานอาหารที่มีสารอาหารครบถ้วนจะช่วยลดความเสี่ยงของการเกิดแผลกดทับได้**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
11	**ท่านรู้หรือไม่ว่าควรทำอย่างไรหากรอยแดงที่เกิดขึ้นบนผิวหนังหลังถูกกดทับไม่จางหายไป**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
12.1	**ท่านใช้เบาะรองนั่ง (เบาะลม เบาะโฟม หรือเบาะชนิดอื่น) หรือไม่**				
	☐ ไม่ใช้	☐ ใช้ (ถ้าใช้ตอบข้อ 12.2)			
12.2	**ท่านรู้วิธีตรวจสอบสภาพของเบาะรองนั่งหรือไม่**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
13	**ท่านรู้หรือไม่ว่าการทำกิจกรรมยามว่างหรือกีฬาบางประเภทอาจเพิ่มความเสี่ยงต่อการเกิดแผลกดทับ**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
14	**ท่านเปลี่ยนท่าขณะนอนบนเตียงบ้างหรือไม่ (ทำเองหรือมีคนช่วย*)**				
	☐ 0: ไม่เคยทำ	☐ 1: ทำบางครั้ง	☐ 2: ทำบ่อยครั้ง	☐ 3: ทำเป็นประจำ	
15.1	**ท่านรู้วิธีจัดท่านอนบนเตียงโดยใช้หมอนวางในตำแหน่งที่ถูกต้องเพื่อป้องกันแผลกดทับหรือไม่**				
	☐ 0: ไม่รู้	☐ 1: พอรู้	☐ 2: รู้ดี	☐ 3: รู้ดีมาก	
15.2	**ท่านได้จัดท่านอนดังข้อ 15.1 หรือไม่ (ทำเองหรือมีคนช่วย*)**				
	☐ 0: ไม่เคยทำ	☐ 1: ทำบางครั้ง	☐ 2: ทำบ่อยครั้ง	☐ 3: ทำเป็นประจำ	

16 **ท่านรู้หรือไม่ว่าสถานการณ์ใดบ้างจะเพิ่มความเสี่ยงต่อการเกิดแผลกดทับ (เช่น มีไข้ กระดูกหัก การอยู่ท่าเดิมนาน ๆ)**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

การป้องกันการเกิดบาดแผล

17 **ท่านรู้หรือไม่ว่าซิป ตะเข็บนูน อุปกรณ์พยุง รองเท้าหรือเสื้อผ้าที่รัดแน่น... เป็นอันตรายได้**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

18 **ท่านรู้หรือไม่ว่าความร้อน (ถ้วยกาแฟร้อน เครื่องทำความร้อน แสงอาทิตย์) และความเย็น (ถุงน้ำแข็ง) เป็นอันตรายต่อผิวหนัง**

☐ 0: ไม่รู้ ☐ 1: พอรู้ ☐ 2: รู้ดี ☐ 3: รู้ดีมาก

19 **ท่านสามารถหลีกเลี่ยงการเกิดแผลถลอกหรือการกระแทกระหว่างที่ท่านเคลื่อนย้ายตัวได้หรือไม่ (ทำเองหรือมีคนช่วย*)**

☐ 0: ไม่เคยทำ ☐ 1: ทำบางครั้ง ☐ 2: ทำบ่อยครั้ง ☐ 3: ทำเป็นประจำ

20 **ท่านตัดเล็บเพื่อป้องกันการเกิดเล็บขบ โดยตัดเล็บตรง ๆ เสมอปลายนิ้ว ไม่ตัดเล็บโค้งเข้าจมูกเล็บหรือตัดลึกเกินไป ตามที่ได้สอนหรือไม่ (ทำเองหรือมีคนช่วย*)**

☐ 0: ไม่เคยทำ ☐ 1: ทำบางครั้ง ☐ 2: ทำบ่อยครั้ง ☐ 3: ทำเป็นประจำ

The revised Skin Management Needs Assessment Checklist

Please mark ✓ next to the most relevant option

Skin Management

1 Do you have a small mirror to inspect your skin? ☐ No ☐ Yes

Skin Checks

2 Do you know how to inspect your skin using a mirror?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

3.1 Do you know which areas of the skin to inspect?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

3.2 Do you know what abnormalities to look for?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

4 Do you know how to palpate your skin to check for pressure injuries that are not open wounds?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

5 Do you inspect your skin as instructed in items 2, 3.1, 3.2, and 4 (either by yourself or with assistance*)?

☐ 0: Never ☐ 1: Sometimes ☐ 2: Often ☐ 3: Regularly

Preventing Pressure Injuries

6 Do you know how to relieve pressure, such as lifting yourself or leaning your body forward?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

7 Do you know how often you should relieve pressure and how long each time should last?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

8 Do you know that smoking increases the risk of developing pressure injuries and delays wound healing?

☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

9	Do you know that sitting on a chair for too long increases the risk of developing pressure injuries? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
10	Do you know that eating a well-balanced diet helps reduce the risk of developing pressure injuries? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
11	Do you know what to do if redness caused by pressure does not go away? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
12.1	Do you use a seat cushion (air cushion, foam cushion, or other)? ☐ No ☐ Yes (If yes, please answer item 12.2)
12.2	Do you know how to check the condition of the seat cushion? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
13	Do you know that some leisure activities or sports might increase the risk of developing pressure injuries? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
14	Do you change positions while lying in bed (either by yourself or with assistance*)? ☐ 0: Never ☐ 1: Sometimes ☐ 2: Often ☐ 3: Regularly
15.1	Do you know how to position yourself in bed using pillows correctly to prevent pressure injuries? ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
15.2	Have you positioned yourself in bed as described in item 15.1 (by yourself or with assistance*) ☐ 0: Never ☐ 1: Sometimes ☐ 2: Often ☐ 3: Regularly
16	Do you know what conditions can increase the risk of developing pressure injuries? (such as fever, bone fractures, or prolonged immobility) ☐ 0: I don't know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well

	Preventing Wounds
17	Do you know that zippers, seams, assistive devices, tight shoes, or tight clothing can harm your skin? ☐ 0: I don’t know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
18	Do you know that heat (e.g., hot coffee, heating devices, sunlight) and cold (e.g., ice packs) can harm your skin? ☐ 0: I don’t know ☐ 1: I know a little ☐ 2: I know well ☐ 3: I know very well
19	Can you avoid causing abrasions or bumps while moving your body? (either by yourself or with assistance) ☐ 0: Never ☐ 1: Sometimes ☐ 2: Often ☐ 3: Regularly
20	Do you cut your nails to prevent ingrown nails by trimming them straight across, not too deeply, as instructed? (either by yourself or with assistance*) ☐ 0: Never ☐ 1: Sometimes ☐ 2: Often ☐ 3: Regularly

**** Please note that this English version was not cross-culturally translated but was only provided to enhance the reader's understanding.**

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Endoscopic Placement of Sengstaken-Blakemore Tube Effectively Reduces Esophageal Rupture Resulting from Tube Malposition: A Propensity Score Analysis

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ABSTRACT

OBJECTIVE This study aimed to evaluate the effectiveness of endoscopically assisted Sengstaken-Blakemore tube placement in reducing the tube malposition rate and resulting complications.

METHODS Data was collected on 45 patients with massive esophageal variceal bleeding who underwent Sengstaken-Blakemore tube placement between January 2011 and June 2016 at our institute. This retrospective study compared the malposition rate, complication rate, and treatment outcome between the conventional blind technique (n = 28) and the endoscopically assisted technique (n = 17), using propensity score analysis to account for differences in baseline characteristics.

RESULTS The rate of malpositioning of the Sengstaken-Blakemore tubes was significantly higher in the conventional blind technique group, while there were no incidents of malpositioning in the endoscopically assisted technique group (25% vs. 0%; p = 0.034). All cases of tube malpositioning in the conventional blind technique group resulted in esophageal perforation, while no perforation occurred in the endoscopically assisted group. The propensity score analysis showed that endoscopic placement was significantly better than the conventional method for esophageal rupture (adjusted RR = 0.78, 95% CI = 0.68–0.91, p = 0.002), but not significantly better for death rate (adjusted RR = 0.68, 95% CI = 0.38–1.21, p = 0.186).

CONCLUSIONS Endoscopic-assisted Sengstaken-Blakemore tube placement can effectively reduce esophageal ruptures resulting from tube malpositioning.

KEYWORDS endoscopic assistance, malposition rate, Sengstaken-Blakemore tube

INTRODUCTION

Since its initial introduction in 1950, Sengstaken-Blakemore tube insertion has become an important procedure for reducing the incidence of massive esophageal variceal bleeding (1, 2). Since that time, many different endoscopic and inventory techniques have emerged to control massive variceal bleeding; however, the use of the Sengstaken-Blakemore tube is still considered the last resort in the control of hemorrhage, especially in cases not responding to other treatments (3, 4). The Sengstaken-Blakemore tube gives favorable results; however, complications from the procedure are frequently reported, primarily resulting from tube malposition. Malposition of the tube can lead to many devastating complications, such as rupture of the esophagus due to gastric balloon inflation or airway obstruction resulting from esophageal balloon insertion. (5-7). To prevent these very serious complications, many maneuvers have been proposed to confirm that the tube is in the proper position. The endoscopic placement of the Sengstaken-Blakemore tube was first proposed in the year 2000 (8). In our institute, this technique has been available, adopted, and used, depending on physician preference, since 2011. This study reviews the treatment outcomes of patients who underwent Sengstaken-Blakemore tube insertion between January 2011 and June 2016. The study includes data from both the conventional and the endoscopically assisted techniques performed during these years.

METHODS

The Research Ethics Committee of the Faculty of Medicine of Chiang Mai University granted approval for this retrospective cohort study, assigning certificate number 284/2016. We examined the electronic medical records of patients on whom the Sengstaken-Blakemore tube had been used at Chiang Mai University Hospital from January 2011 to June 2016. We gathered demographic information on the patients, including gender, age, preexisting conditions, and current medications. We also obtained medical data including vital signs, the severity of shock, manifestations of chronic liver disease, the technique of Sengstaken-Blakemore tube insertion used, endoscopic findings and interventions, pharmacological treatment involving a proton pump inhibitor and a somatostatin analog, and the treatment outcomes. The patient data was categorized into two groups according to the Sengstaken-Blakemore tube insertion technique: conventional or endoscopic-guided.

Procedure

Before starting the procedure, an endotracheal tube was inserted for airway protection. All patients received a fluid resuscitation consisting of a crystalloid solution. If the patient did not respond to the initial crystalloid solution or if their Hct was less than 21%, we performed a transfusion of packed red cells. We corrected coagulation abnormalities and thrombocytopenia as needed.

The conventional technique involves inserting the tube completely through the nostril. Auscultation of the epigastric area confirms proper tube positioning. Once we confirmed the correct tube position, we inflated the gastric balloon with 50 ml of air and gently pulled back the tube until the gastric balloon snugly fit the esophagogastric junction. Next, we continued to inflate the gastric balloon until it reached a total volume of 250 ml. A sphygmomanometer measured the pressure of the esophageal balloon at 40 mmHg only when the gastric balloon failed to control the bleeding. Once the procedure was complete, we inserted a number 12 nasogastric (NG) through the other nostril to a level of 25 cm to drain saliva. After that procedure, we performed a chest x-ray to confirm the correct placement of the tube. We kept the balloon inflated for 24 hours. After that, if the bleeding was under control, we removed the Sengstaken-Blakemore tube. However, if the bleeding was still ongoing, we re-inflated the balloon after 30 minutes of deflation. We removed the Sengstaken-Blakemore tube 48 hours after the insertion regardless of whether the bleeding had stopped or not.

The endoscopic guided Sengstaken-Blakemore tube insertion procedure was performed under general anesthesia with endotracheal tube intubation as follows:

1. After an endoscopic examination discovered variceal bleeding that had failed to be controlled by endoscopic methods, the Sengstaken-Blakemore tube was checked with air inflation to examine whether there was any leakage.
2. We inserted the tube into the nostril and passed it through to the hypopharynx.
3. We inserted an endoscope into the patient's mouth through the mouth gag. We used a 9.8-mm-diameter endoscope to facilitate insertion through the hypopharynx area. We also briefly deflated the endotracheal tube balloon during this step to reduce the pressure at the hypopharynx. When inserting the endoscope posterior to the esophageal inlet, we selected a path that passed through one side of the corniculate cartilage, where the Sengstaken-Blakemore tube was already passing. We maintained direct visualization of the upper esophageal sphincter while advancing the endoscope (Figure 1).

4. We inserted the tube and endoscope simultaneously through the esophagus which facilitated the tube insertion. In most cases, this step required neither grasping nor fixing.

5. After the endoscope had entered the stomach, the endoscopist performed a J turn, after which the gastric balloon of the Sengstaken-Blakemore tube would normally be visible (Figure 2).

6. We inflated the gastric balloon under direct visualization before withdrawing the endoscope (Figure 3).

7. The procedure for inflating both the gastric and esophageal balloons followed the same steps as the conventional procedure. An NG tube as a salivary drain was placed in the same fashion. We routinely performed a chest x-ray after the procedure to confirm the proper position. The protocol for the removal of the Sengstaken-Blakemore tube was identical to the conventional technique.

Statistical method

Statistical analysis was done using the STATA program version 16.0. The student's t-test and rank-sum test were used in the analysis of continuous data, and Fisher's exact test was used for categorical data.

As a retrospective study, the two contrast groups were observational and not randomly allocated. Direct comparisons of the outcomes between the two contrast groups would have likely resulted in biased estimates. Two potential sources of bias, confounding by indication and confounding by contraindication, would likely have affected the true association between insertion techniques and outcomes (esophageal rupture and mortality rate). The use of the propensity score method enabled the investigators to create contrast groups that more accurately measured the relationship between treatment and outcomes. The propensity score was estimated as a surrogate of the likelihood or the probability of being assigned to each group. It was calculated in the form of logit as a function of factors (age, shock grading, and Child-Pugh) most likely to influence the likelihood of being assigned to each insertion technique. The calculated propensity score was then used as a covariate to control for confounding by indication and confounding by contraindication in the final model. The effect of each insertion technique on the results of treatment was analyzed by log-risk regression, which was adjusted by propensity score modeling.

RESULTS

This study included a total of 45 patients with massive esophageal variceal bleeding who underwent Sengstaken-Blakemore tube placement. Twenty-eight patients underwent the conventional technique, while 17 patients underwent the endoscopically assisted technique. In the endoscopically guided group, the mean age of the patients was slightly higher than that of the conventional group (58.8±14.7 vs. 50.0±13.6 years; p = 0.046). Overall, there was no statistically significant difference between the patients in the two groups regarding other baseline characteristics. Most patients were males, presenting with a high grade of shock and decompensated liver function. All patients fell into a high-risk category when stratified using the Rockall score. Some of the patients in both groups had previously undergone an endoscopic examination, which identified most of them as high-risk (Grade 2, 3 in quantitative guidelines, > 5 mm) for the variceal lesion, as per the American Association for the Study of Liver Disease (AASLD) practice guidelines (9). The majority of fluid used in resuscitation in both groups of patients was a crystalloid solution, and the amounts used were not statistically different. Patients in the endoscopic group and conventional group received similar medical treatment: 58.8% vs. 82.1% somatostatin analogue, 94.1% vs. 85.7% tranexamic acid, and 35.3% vs. 48.2% vasopressor. There were no statistically significant differences in these data. Patients in both groups had anemia. Both groups had a high level of BUN and low levels of HCO_3, which are results of hypovolemic shock. Patients received on average two units of PRC and four units of fresh frozen plasma, equal in both groups (Table 1).

In the endoscopic insertion group, the 17 patients underwent an endoscopic examination first, and then the endoscopic-guided Sengstaken-Blakemore insertion. The median duration from the start of the endoscopic examination to full balloon insufflation was 48 minutes, with a range of 10 to 155 minutes. There were no complications during the procedures. Most patients were at a high grade of variceal, distributed between Grades

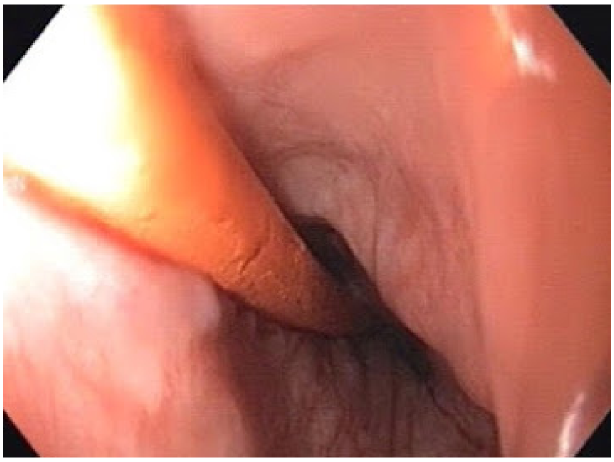

Figure 1. Sengstaken-Blakemore tube in the esophagus after passing the hypopharynx and upper esophageal sphincter

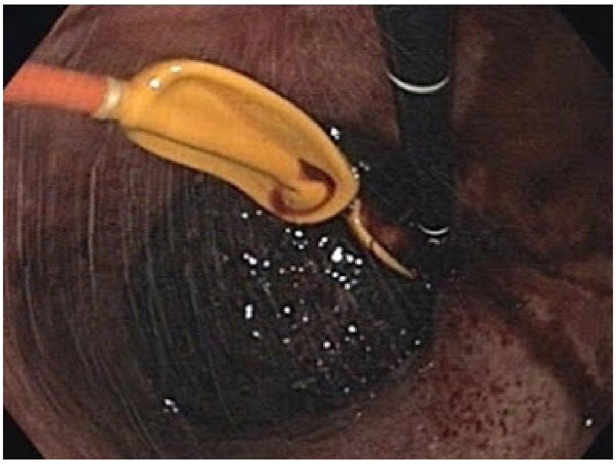

Figure 2. Gastric balloon seen after performing an endoscopic J turn

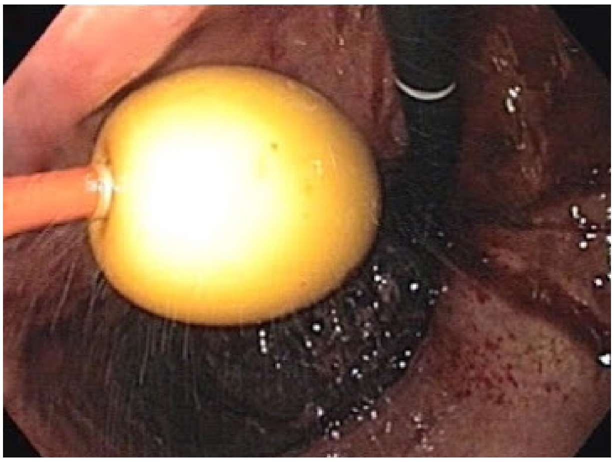

Figure 3. Gastric balloon inflation under direct visualization

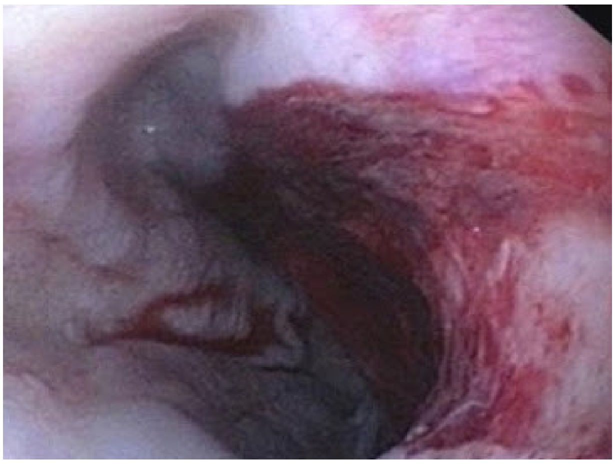

Figure 4. Esophageal perforation from a Sengstaken-Blakemore tube (muscular layer completely torn with visible periesophageal adventitia)

2 and 3 (60% vs 40%); data were not recorded in seven cases. Most patients in both groups also had gastric varices, with the majority having gastro-oesophageal varice (GOV) type 1 (76.9%). The median blood loss as recorded by the anesthesiologist during the procedure was 300 ml. This group of patients had a median of two units of PRC transfusion, and almost all patients had no FFP or platelet transfusion (Table 2).

A post-procedure portable chest x-ray revealed malposition of the Sengstaken-Blakemore tube in seven cases in the conventional group (25% vs. 0%, p = 0.034), a significantly higher rate than in the endoscopic group. In the group with a malpositioned tube, all patients ultimately had an esophageal perforation. The treatment outcomes following the Sengstaken-Blakemore tube procedure for temporary bleeding control showed no statistical differences between groups. The overall bleeding control rate was 46.7%. There was a very high mortality rate, 52.9% vs. 67.9% in the endoscopic group and conventional group, respectively (p = 0.357). The leading cause of death was hemorrhagic shock (Table 3).

The association between prognostic factors and the result of treatment was analyzed. In the endoscopically guided group, there was a lower mortality rate; however, this was not statistically significant. The only prognostic factor that showed a significant association is the Child-Pugh score (p = 0.003). The Child-Pugh C group had the highest mortality rate at 79.3% (Table 4).

Child-Pugh is an important parameter in creating a propensity score. The propensity score analysis indicated a significant superiority in avoiding esophageal rupture with endoscopic placement compared to the conventional technique (adjusted RR = 0.78, 95% CI = 0.68-0.91, p

Table 1. Baseline characteristics of patients before Sengstaken-Blakemore tube insertion

Characteristics	Endoscopic guided technique (n=17)	Conventional guided technique (n=28)	*p*-value
Age (years), mean±SD	58.8±14.7	50.0±13.6	0.046
Gender, n (%)			0.350
Male	14 (82.4)	26 (92.9)	
Female	3 (17.6)	2 (7.1)	
Shock grade, n (%)			1.000
Grade 1	1 (5.9)	3 (10.7)	
Grade 2	2 (11.8)	2 (7.1)	
Grade 3	9 (52.9)	14 (50.0)	
Grade 4	5 (29.4)	9 (32.1)	
Child-Pugh, n (%)			1.000
Class A	1 (5.9)	1 (3.6)	
Class B	5 (29.4)	9 (32.1)	
Class C	11 (64.7)	18 (64.3)	
Rockall score (pre-endoscopic)			0.137
0-2 (low risk)	2 (11.8)	0 (0.0)	
3-7 (high risk)	15 (88.2)	28 (100.0)	
Previous endoscopic findings: esophageal variceal grading, n (%)			0.752
Grade 1	1 (12.5)	5 (27.8)	
Grade 2	3 (37.5)	4 (22.2)	
Grade 3	4 (50.0)	9 (50.0)	
Fluid resuscitation in first 24 hrs. (mL), median (range)			
Crystalloid	1,500 (100-4,000)	1,000 (0-5,180)	0.176
Colloid	0 (0-4,000)	0 (0-1,500)	0.920
Medication, n (%)			
Somatostatin analogue	10 (58.8)	23 (82.1)	0.163
Tranexamic acid	16 (94.1)	24 (85.7)	0.635
Vasopressor	6 (35.3)	13 (48.2)	0.535
Laboratory results, median (range)			
Hb	7.1 (4.0-10.5)	7.4 (2.7-11.9)	0.609
Hct	21.7 (12.2-31.4)	23.1 (9.2-36)	0.532
WBC	9,070 (3,590-182,000)	9,740 (1,380-19,700)	0.833
Platelets	126,000 (30,000-288,000)	95,500 (12,000-298,000)	0.198
PT	17.3 (12.1-26.9)	20.3 (12.3-90.2)	0.761
PTT	36.8 (24.5-132.9)	36.9 (23.5-200.0)	0.935
INR	1.6 (1.1-2.6)	2.0 (1.2-8.2)	0.468
BUN	24 (6-86)	26.5 (7-90)	0.851
Creatinine	1.3 (0.7-6.8)	1.4 (0.6-10.5)	0.833
HCO_3	15 (8-21)	16.5 (6-35)	0.264
Blood products received (units), median (range)			
PRC	2 (1-5)	2 (0-9)	0.691
FFP	4 (0-8)	4 (0-8)	0.660
Platelets	0 (0-10)	2 (0-20)	0.667

= 0.002) but a non-significant superiority in mortality rate (adjusted RR = 0.68, 95% CI = 0.38-1.21, p = 0.186) (Table 5).

DISCUSSION

End-stage liver disease can cause bleeding from esophageal varices, a devastating emergency condition with a grave prognosis. Even with proper management, an exsanguinous, uncontrolled hemorrhage can lead to patient mortality. Introduced as a sole therapy for dealing with variceal hemorrhage in 1950 (1), the Sengstaken-Blakemore tube is still used as a rescue procedure in cases when the physician cannot stop the

Table 2. Clinical data for endoscope-guided procedure patients

Variables	Endoscopic guided technique (n=17)
Duration (minutes), median (range)	48 (10-155)
Complications, n (%)	0 (0.0)
Endoscopic findings	
Esophageal variceal grading, n (%)	
Grade 1	0 (0.0)
Grade 2	6 (60.0)
Grade 3	4 (40.0)
Sarin classification, n (%)	
GOV1	10 (76.9)
GOV2	3 (23.1)
Blood loss during procedure, (ml) median (range)	300 (30-2,000)
Blood product received during the procedure (units), median (range)	
PRC	2 (0-6)
FFP	0 (0-6)
Platelets	0 (0-4)

GOV, gastro-oesophageal varice

Table 3. Results of Sengstaken-Blakemore Tube Placement Hemorrhagic Control and Complications

Variables	Endoscopic guided technique (n=17)	Conventional guided technique (n=28)	*p*-value
Proper positioning of the tube, n (%)			0.034
Good positioning	17 (100.0)	21 (75.0)	
Malpositioning	0 (0.0)	7 (25.0)	
Shock grading at 24 hrs. after the procedure, n (%)			0.389
Grade 1	10 (58.8)	11 (39.3)	
Grade 2	2 (11.8)	2 (7.1)	
Grade 3	0 (0.0)	3 (10.7)	
Grade 4	5 (29.4)	12 (42.9)	
Blood products received after the procedure (in a 24 hrs. period) (units), median (range)			
PRC	2 (0-9)	2 (0-10)	0.709
FFP	4 (0-6)	4 (0-16)	0.583
Plt	4 (0-11)	0 (0-10)	0.013
Medication use, n (%)			
Somatostatin analogue	15 (88.2)	24 (85.7)	1.000
Tranexamic acid	16 (94.1)	26 (92.9)	1.000
Vasopressor	7 (41.2)	16 (57.1)	0.365
Results of laboratory follow-up at 24 hrs. after procedure, median (range)			
Hb (g/dL)	8.4 (4.3-11.2)	7.4 (2.1-10.6)	0.178
Hct (%)	25.8 (15.6-35.2)	22.8 (6.8-32.3)	0.145
WBC (cells/mm^3)	11,300 (2,200-27,400)	11,890 (2,450-19,220)	0.662
Platelets (cells/mm^3)	106,000 (10,400-228,000)	88,000 (26,000-203,000)	0.435
PT (sec)	17.9 (11.8-27.1)	16.9 (11.5-200.0)	0.888
PTT (sec)	35.1 (24.7-88.7)	35.2 (20.4-200.0)	0.759
INR	1.7 (1.1-2.6)	1.6 (1.1-10.0)	0.828
BUN (mg/dL)	27 (10-81)	31 (6-93)	0.898
Creatinine (mg/dL) (mEq/L)	1.6 (0.5-6.2)	1.6 (0.4-11.4)	0.847
HCO_3 (mEq/L)	16 (6-22)	18 (3-38)	0.563
Complication (esophageal rupture), n (%)	0 (0.0)	7 (25.0)	0.034
Length of hospital stay (days), median (range)	9 (1-30)	6 (1-120)	1.000
Result of treatment (%)			0.357
Discharge	8 (47.1)	9 (32.1)	
Death	9 (52.9)	19 (67.9)	
Cause of death, n (%)			0.371
Hemorrhagic	5 (55.6)	15 (79.0)	
Sepsis	4 (44.4)	4 (21.0)	

Table 4. Association between prognostic factors and results of treatment

Prognostic factors	Result of treatment, n (%)		*p*-value
	Death (n=28)	Discharge (n=14)	
Technique			0.357
Endoscopic-guided technique	9 (52.9)	8 (47.1)	
Conventional guided technique	19 (67.9)	9 (32.1)	
Child-Pugh			0.003
Class A	0 (0.0)	2 (100.0)	
Class B	5 (35.7)	9 (64.3)	
Class C	23 (79.3)	6 (20.7)	
Shock grading			0.226
Grade 1	2 (50.0)	2 (50.0)	
Grade 2	1 (25.0)	3 (75.0)	
Grade 3	14 (60.9)	9 (39.1)	
Grade 4	11 (78.6)	3 (21.4)	
Rockall score (pre-endoscopic)			1.000
0-2 (low risk)	1 (50.0)	1 (50.0)	
3-7 (high risk)	27 (62.8)	16 (37.2)	
Esophageal perforation, n (%)			1.000
No	24 (63.2)	14 (36.8)	
Yes	4 (57.1)	3 (42.9)	

Table 5. Univariable and multivariable risk ratio of esophageal rupture and mortality rate after sengstaken-blakemore tube insertion, adjusted by propensity score analysis

Outcomes	Univariable analysis		Multivariable analysis	
	Crude RR (95% CI)	*p*-value	Crude RR (95% CI)	*p*-value
Esophageal rupture				
Insertion technique (endoscopic guided over conventional)	0.80 (0.70-0.91)	0.001	0.78 (0.68-0.91)	0.002
Mortality rate				
Insertion technique (endoscopic guided over conventional)	0.78 (0.46-1.31)	0.351	0.68 (0.38-1.21)	0.186

RR, risk ratio; CI, confidence interval

bleeding with an endoscopic intervention (10). In some rural areas where endoscopy is not available, the tube remains the sole treatment. The results of treatment with a Sengstaken-Blakemore tube vary. Previous studies have reported that initial bleeding control was achieved at a rate of 80.0-91.5%. However, rebleeding occurred frequently in almost half of the patients. Overall, definite control of bleeding was achieved at a rate of 47.7-67.0% (3, 4). In our study, rebleeding occurred in 53.3% of patients, a rate comparable to that found in previous studies.

Unfortunately, complications associated with Sengstaken-Blakemore tube insertion have continued to be reported. Various devastating complications, ranging from acute airway obstruction to esophageal perforation (Figure 4), can potentially occur due to the malposition of the initial placement or subsequent migration. These complications often lead to more complex situations requiring invasive intervention or surgery. In this group of patients, there is usually a higher rate of morbidity and mortality (5-7, 11).

In response to the potential severe problems and challenges related to Sengstaken-Blakemore tube implantation, numerous alternative approaches have been suggested, including the guidewire-assisted technique, which involves confirming the guidewire's position via fluoroscopy, followed by the insertion of a Sengstaken-Blakemore tube over the guidewire under fluoroscopic observation. Authors of some studies have suggested employing ultrasound, commonly utilized in emergency clinics, as a verification method for tube placement that produces favorable outcomes. The endoscopic guiding approach has also been examined and shown to produce positive results (8, 12, 13).

According to variceal bleeding treatment guidelines, early endoscopic treatment of bleeding is highly recommended (9). Therefore, the placement of the Sengstaken-Blakemore tube should be employed only after the use of the endoscopic procedure has failed to achieve bleeding control. One variation in the endoscopic technique involves using an endoscopic grasper to directly grab the tube or attaching a suture loop at the tube's tip to serve as a grasping point (8, 14). Our team discovered that we could gently insert the Sengstaken-Blakemore tube simultaneously with the endoscope without using a grasping or fixing method.

In our study, we found no statistically significant difference between the endoscopic-guided technique and the conventional technique regarding the patient's hemodynamic status at 24 hours. This includes bleeding control (endoscopic guided vs. conventional, 58.8% vs. 39.3%, p = 0.389) and overall mortality (52.9% vs. 67.9%, p = 0.357). This might be due to the poor initial condition of most of the patients in our study. Most patients in both groups were categorized as having Child-Pugh C cirrhosis, which is associated with a high risk of rebleeding according to the Rockall score and a high grade of shock.

Due to the direct visualization of the gastric balloon in the stomach, the endoscopic-guided technique achieved proper tube placement at a significantly higher rate than the conventional technique (100% vs. 75%, p = 0.034). The endoscopic procedure, which included both endoscopic diagnosis and therapy, took an average of 48 minutes to complete (range 10-155 minutes). The mortality rate for the endoscopically guided technique was slightly but non-significantly lower, which could be attributed to a lower rate of complications. Our study found a generally higher rate of complications than previous reports (25% vs 7-10%), potentially due to the fact that most often a general practitioner and an intern rather than a gastroenterologist performed the insertions in the conventional group (3, 4). The endoscopic procedure does have limitations, including the necessity to move the patient to the endoscopic suite, which requires the patient's condition to be relatively stable, as well as the availability of the endoscopist. In cases of significant hemorrhage where patients do not respond to resuscitation or in hospitals without endoscopic facilities, traditional techniques remain the primary treatment approach.

For both variceal and non-variceal bleeding, endoscopy is a standard procedure that serves both diagnostic and therapeutic purposes, and it should always be the initial therapy of choice (9, 15). The insertion of a Sengstaken-Blakemore tube under direct visualization of endoscopy should be done immediately after a diagnosis of variceal bleeding is confirmed and endoscopic therapy has failed to stop bleeding. Performing this procedure as part of the endoscopic procedure could potentially prevent unnecessary insertions and complications.

Limitations

The retrospective cohort study design may have been subject to selection bias. Additionally, given the high morbidity rate with variceal hemorrhage, the therapeutic interventions given to the patients may not have had a significant impact on outcomes.

CONCLUSIONS

The endoscopic guided technique can improve the accuracy of tube positioning and could potentially serve as an optional treatment for Sengstaken-Blakemore tube insertion.

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CONFLICTS OF INTEREST

There are no potential financial and non-financial conflicts of interest.

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