ORIGINAL ARTICLE

Aldosterone-to-Potassium Ratio for Predicting Lateralized Primary Aldosteronism in Patients with Unilateral Adrenal Nodules

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Background: Adrenal vein sampling (AVS) is the standard method for subtyping primary aldosteronism (PA) and selecting candidates for adrenalectomy. However, its application is limited by restricted availability and the risk of catheterization failure, which requires experienced operators. Markedly elevated aldosterone levels, severe hypokalemia, and unilateral adrenal nodules are commonly observed in lateralized PA and may aid in subtyping.

Objective: To evaluate the aldosterone-to-potassium ratio (APR) for predicting lateralized PA in patients with unilateral adrenal nodules.

Materials and Methods: The present study was a retrospective study that included PA patients with unilateral adrenal nodules and successful AVS between January 2012 and December 2024. Lateralized and bilateral PA were classified based on AVS. The APR was compared between subtypes, and its utility for subtyping PA was assessed.

Results: Of 85 patients, the median age was 56 years and 53% were men. Fifty-one patients (60%) had lateralized PA and 34 (40%) had bilateral PA. Serum potassium was lower in patients with lateralized PA compared to those with bilateral PA at 2.8 versus 3.2 mmol/L ($p<0.01$), and plasma aldosterone concentration was higher at 29 versus 18 ng/dL ($p<0.01$). The median APR was significantly higher in the lateralized group at 12.4 versus 6.2 ng/dL:mmol/L ($p<0.01$). An APR threshold of 12 predicted lateralized PA with an AUC of 0.796 ($p<0.001$), yielding 57% sensitivity and 91% specificity.

Conclusion: The APR may serve as a practical tool for predicting lateralized PA in patients with unilateral adrenal nodules. Its diagnostic performance supports its role as a supplementary method for subtyping when AVS is not feasible.

Keywords: Adrenal nodule; Aldosterone; Potassium; Primary aldosteronism; Adrenal vein sampling

Received 6 May 2025 | Revised 26 May 2025 | Accepted 30 May 2025

J Med Assoc Thai 2025;108(7):588-95

Website: http://www.jmatonline.com

Driven by autonomous aldosterone production from the adrenal cortex, primary aldosteronism (PA) is now established as a major cause of secondary hypertension[1], with a prevalence estimated at 5% to 10% among hypertensive patients[2-4], and reaching up to 20% to 30% in those with resistant hypertension[5,6]. It is also associated with increased cardiovascular and renal morbidity and mortality[7,8]. PA is commonly classified into two major subtypes, unilateral PA, typically caused by an aldosterone-producing adenoma (APA), and bilateral PA. Accurate subtyping is essential for guiding appropriate treatment and optimizing clinical outcomes. While unilateral PA can be cured with adrenalectomy, bilateral PA usually requires long-term treatment with mineralocorticoid receptor antagonists[9].

Adrenal vein sampling (AVS) is the gold standard for subtyping PA[10]. Although the procedure is invasive, costly, and technically challenging, previous data have indicated failure rates of up to 70%[11]. More recent multicenter studies from experienced referral centers continue to show that approximately 20% of procedures remain unsuccessful[12]. In addition, bilateral aldosterone suppression (BAS) is not uncommon and may complicate AVS interpretation[13]. Moreover, AVS is not widely available in Thailand due to limited access

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How to cite this article:

Vibhatavata P, Watanakitsiri W. Aldosterone-to-Potassium Ratio for Predicting Lateralized Primary Aldosteronism in Patients with Unilateral Adrenal Nodules. J Med Assoc Thai 2025;108:588-95.

DOI: 10.35755/jmedassocthai.2025.7.588-595-03104

to interventional radiology.

In patients with unilateral PA, certain clinical features have been identified as predictive indicators. These include severe hypokalemia, markedly elevated aldosterone concentrations, and unilateral adrenal nodules with a normal-appearing contralateral adrenal gland on imaging[14-18]. However, non-functioning adrenal incidentalomas are frequently encountered in the general population, with a reported prevalence of approximately 3% to 10% in adults[19-21]. Therefore, the presence of an adrenal nodule does not necessarily indicate unilateral aldosterone excess, as individuals with bilateral PA may coincidentally harbor non-functioning adrenal adenomas.

To enhance predictive accuracy, integrating biochemical markers with imaging features may improve the identification of patients with lateralized diseases. The authors hypothesized that, among PA patients with unilateral adrenal nodules, a high aldosterone-to-potassium ratio (APR) would be associated with lateralized PA, as determined by AVS, which served as the reference standard for subtyping. The present study aimed to compare the APR between patients with lateralized and bilateral PA and evaluate its diagnostic value in subtype classification.

Materials and Methods

Study design and participants

The present study was a retrospective study that included all confirmed PA patients at Thammasat University Hospital between January 2012 and December 2024. The study was approved by the Human Research Ethics Committee of Thammasat University (MTU-EC-IM-0-056/67).

Adult patients were eligible for inclusion if they had a confirmed diagnosis of PA according to the Endocrine Society Guidelines[10,22], showed a positive result on either the saline infusion test or the captopril challenge test, or fulfilled confirmatory criteria defined by an aldosterone concentration exceeding 20 ng/dL together with suppressed renin and spontaneous hypokalemia, and had unilateral adrenal nodules on adrenal computed tomography (CT). Patients were excluded if AVS was not performed, catheterization of both adrenal veins (AV) was unsuccessful, or AVS results indicated BAS. Patient demographics, antihypertensive medication doses as calculated using the WHO ATC/DDD index[23], biochemical parameters, potassium supplementation dose, imaging findings, AVS results, follow-up records, and treatment outcomes were retrospectively reviewed. Plasma aldosterone concentration (PAC) and direct renin concentration (DRC) were measured using a chemiluminescent immunoassay on the DiaSorin Liaison® Analyzer. For patients evaluated prior to October 2017, renin was measured as plasma renin activity (PRA) using a Siemens radioimmunoassay, as previously reported[24]. Medications known to interfere with the renin-aldosterone system were discontinued for two to six weeks prior to PAC and renin screening. Adrenal CT was performed using axial imaging at 3-mm intervals, including pre-contrast, arterial, portal venous, and delayed contrast phases, with multiplanar reconstruction. Clinical and biochemical outcomes after adrenalectomy were assessed based on the Primary Aldosteronism Surgical Outcome (PASO) consensus[25], which classifies outcomes as complete, partial, or absent.

Aldosterone-to-potassium ratio

To calculate the APR, the highest recorded PAC during the screening process was used. This value was typically obtained after correction of hypokalemia and adjustment of medications that could interfere with PAC. In accordance with the authors' institutional protocol, interfering antihypertensive agents were replaced with verapamil SR, alpha-blockers, or hydralazine as recommended by the Endocrine Society Guidelines[10]. APR was calculated by dividing the highest recorded PAC by the lowest serum potassium level measured before potassium supplementation.

Adrenal vein sampling

Sequential AVS was performed at least 30 minutes after initiating a continuous intravenous infusion of synthetic adrenocorticotropin of cosyntropin at a rate of 50 µg/hour. Successful catheterization was determined using the selectivity index (SI), defined as the ratio of cortisol concentration in the AV to that in the peripheral circulation. An SI greater than 5 was considered indicative of successful cannulation. The lateralization index (LI), calculated as the ratio of the aldosterone-to-cortisol (A/C) concentration in the dominant AV to that in the non-dominant AV, was used to classify PA subtype. An LI of 4 or more indicated lateralized PA, while an LI of less than 4 was consistent with bilateral PA. The contralateral index (CI) was defined as the ratio of the A/C concentration in the non-dominant AV to that in the peripheral vein. BAS was defined as AV-to-peripheral A/C ratios of less than 1 in both AVs.

Statistical analysis

A sample size of 32 patients per group was estimated to provide 80% power to detect a significant difference in outcomes between patients with lateralized and bilateral PA. Categorical variables were presented as numbers and percentages, while continuous variables were reported as medians with interquartile ranges (IQRs). Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, as appropriate. The Mann-Whitney U test was used to compare continuous variables. Univariable and multivariable logistic regression analyses were conducted to identify factors associated with lateralized PA, with results expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). The diagnostic performance of the APR was assessed using receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using GraphPad Prism version 10.2.3 (GraphPad Software, Inc., Boston, MA), and a two-sided p-value of less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of participants

Of the 193 patients with confirmed PA, 116 had unilateral adrenal nodules on adrenal CT. Among these, 14 did not undergo AVS, 14 had unsuccessful AV cannulation, and three showed BAS on AVS. Therefore, 85 patients were included in the final analysis, comprising 51 with lateralized PA and 34 with bilateral PA (Figure 1). In all patients with lateralized PA, CT findings and AVS results were concordant regarding the side of disease involvement.

Demographic and clinical characteristics of the study participants are summarized in Table 1. The median age was 56 years [IQR 45 to 62], and 53% were men, with no significant differences between the two groups. The overall antihypertensive treatment burden, as reflected by the ATC/DDD index, was comparable between groups. Diuretics were rarely used and only one patient in the bilateral group received it during episodes of hypokalemia. The size of adrenal nodules was comparable between the two groups. Patients with lateralized PA had significantly lower serum potassium levels compared to those with bilateral PA of 2.8 [2.4 to 3.0] versus 3.2 [3.0 to 3.5] mmol/L (p<0.01). The required dose of oral potassium supplementation was significantly higher in the lateralized PA group (p<0.01). Renin was measured by either DRC or PRA. In the lateralized PA group, 35 patients had DRC and 16 had PRA. In the bilateral PA group, 25 had DRC, seven had PRA, and two underwent both measurements. PAC was significantly higher in the lateralized group at 29 [23 to 53] versus 18 [16 to 29] ng/dL (p<0.01), while DRC was lower (p<0.01). BMI was higher in patients with bilateral PA (p=0.03).

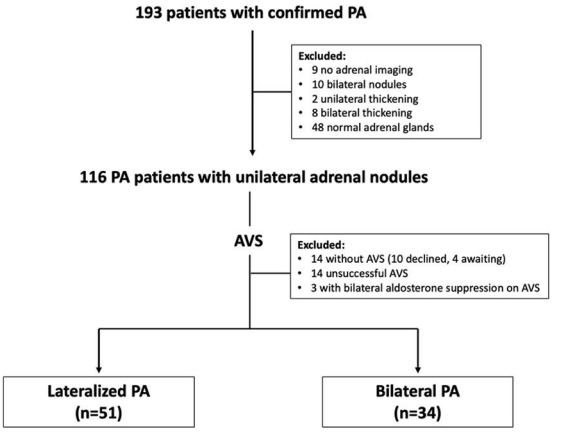

Figure 1. Study flow.

PA, primary aldosteronism; AVS, adrenal vein sampling

Univariable analysis identified a lower BMI, reduced serum potassium, suppressed DRC, and elevated PAC as factors associated with lateralized PA. Of these, only low serum potassium and high PAC remained significant in the multivariable analysis (Table 2).

Aldosterone-to-potassium ratio and PA subtypes

The median APR was significantly higher in patients with lateralized PA compared to those with bilateral PA at 12.4 [7.7 to 22.2] versus 6.2 [4.3 to 10.2] ng/mL:mmol/L (p<0.01) (Figure 2A). When categorized into three groups based on APR values, with groups of less than 6, 6 to 12, and more than 12, the distribution of PA subtypes showed a clear trend across these categories (Figure 2B). Among those with an APR of less than 6, most had a bilateral PA at 74%. In the intermediate range of APR 6 to 12, the proportions of lateralized and bilateral PA were nearly equal at 55% versus 45%. For those with APR greater than 12, lateralized PA predominated, accounting for 90% of cases. The area under the ROC curve (AUC) for APR in predicting lateralized PA was 0.796 (95% CI 0.704 to 0.888, p<0.001) (Figure 3). An APR threshold above 12 yielded 57% sensitivity and 91% specificity. To achieve 100% specificity, an APR greater than 14.5 was required.

Table 1. Demographics and clinical characteristics of study participants

	Total (n=85)	Lateralized PA (n=51, 60%)	Bilateral PA (n=34, 40%)	p-value
Age (years); median [IQR]	56 [45 to 62]	56 [45 to 61]	56 [45 to 64]	0.58
Men; n (%)	45 (53)	27 (53)	18 (53)	0.99
Co-morbidities; n (%)				
Left ventricular hypertrophy	23 (27)	16 (31)	7 (21)	0.32
Cerebrovascular disease	12 (14)	5 (10)	7 (21)	0.21
Diabetes mellitus	17 (20)	7 (14)	10 (29)	0.10
Coronary artery disease	5 (6)	5 (10)	0 (0)	0.08
Heart failure	2 (2)	1 (2)	1 (3)	>0.99
Atrial fibrillation	1 (1)	1 (2)	0 (0)	>0.99
Body mass index (kg/m^2); median [IQR]	26.5 [24.1 to 28.8]	25.6 [23.8 to 27.8]	27.8 [24.3 to 30.0]	0.03
Systolic blood pressure (mmHg); median [IQR]	148 [138 to 157]	147 [139 to 155]	148 [138 to 159]	0.50
Diastolic blood pressure (mmHg); median [IQR]	89 [82 to 97]	90 [83 to 99]	88 [81 to 92]	0.40
Medications use during hypokalemia; n (%)				
Calcium channel blockers	71 (84)	45 (88)	26 (76)	0.23
Alpha blockers	47 (55)	29 (57)	18 (53)	0.82
Direct arterial vasodilators	52 (61)	34 (67)	18 (53)	0.20
ACE-inhibitors/ARBs	10 (12)	5 (10)	5 (15)	0.51
Beta blockers	4 (5)	2 (4)	2 (6)	0.99
Diuretics	1 (1)	0 (0)	1 (3)	0.40
ATC/DDD index; median [IQR]	3.2 [2.0 to 4.7]	3.3 [2.0 to 5.3]	3.0 [2.0 to 4.6]	0.78
Creatinine (mg/dL); median [IQR]	0.86 [0.76 to 1.12]	0.87 [0.70 to 1.13]	0.86 [0.80 to 1.12]	0.78
eGFR (mL/minute/1.73 m^2); median [IQR]	83 [70 to 102]	82 [70 to 101]	88 [67 to 103]	0.74
Lowest serum potassium (mmol/L); median [IQR]	2.9 [2.6 to 3.2]	2.8 [2.4 to 3.0]	3.2 [3.0 to 3.5]	<0.01
Oral potassium supplement (mEq/day); median [IQR]	40 [20 to 120]	80 [40 to 120]	20 [0 to 40]	<0.01
PAC (ng/dL); median [IQR]	26 [17 to 46]	29 [23 to 53]	18 [16 to 29]	<0.01
PRA (ng/mL/hour); median [IQR]	0.3 [0.2 to 0.8]	0.3 [0.1 to 0.7]	0.7 [0.2 to 0.9]	0.24
DRC (μIU/mL); median [IQR]	3.0 [1.1 to 7.7]	1.5 [0.9 to 4.2]	5.0 [3.3 to 8.0]	<0.01
Lipid rich adenoma; n (%)	53 (62)	34 (67)	19 (56)	0.31
Size of adrenal nodule (mm); median [IQR]	14 [11 to 18]	15 [12 to 19]	13 [10 to 17]	0.07
Lateralization index; median [IQR]	6.0 [2.0 to 23.8]	19.4 [8.6 to 48.2]	1.7 [1.3 to 2.4]	<0.01
Contralateral index; median [IQR]	0.4 [0.2 to 1.1]	0.2 [0.1 to 0.3]	1.2 [0.7 to 2.3]	<0.01

IQR=interquartile range; PA=primary aldosteronism; ATC/DDD=total daily dose of antihypertensive agents; eGFR=estimated glomerular filtration rate; PAC=plasma aldosterone concentration; PRA=plasma renin activity; DRC=direct renin concentration; ACE=angiotensin converting enzyme; ARBs=angiotensin receptor blockers

Table 2. Univariable and multivariable analysis for factors associated with lateralized PA

Parameters	Univariable analysis			Multivariable analysis		
	β-coefficient	OR (95% CI)	p-value	β-coefficient	OR (95% CI)	p-value
BMI	−0.09	0.91 (0.82 to 1.00)	0.08			
Serum potassium	−2.74	0.06 (0.01 to 0.22)	<0.01	−2.59	0.07 (0.01 to 0.28)	<0.01
PAC	0.06	1.06 (1.03 to 1.11)	<0.01	0.06	1.06 (1.02 to 1.11)	<0.01
DRC	−0.09	0.92 (0.81 to 1.03)	0.15			

PA=primary aldosteronism; BMI=body mass index; PAC=plasma aldosterone concentration; DRC=direct renin concentration; OR=odds ratio; CI=confidence interval

Postoperative outcomes in the lateralized PA group

Of the 51 patients with lateralized PA, 43 underwent adrenalectomy. Clinical and biochemical outcomes are summarized in Table 3. Complete clinical success was achieved in 49% of these patients. Biochemical outcomes were available for 40 patients, with 88% achieving complete biochemical success.

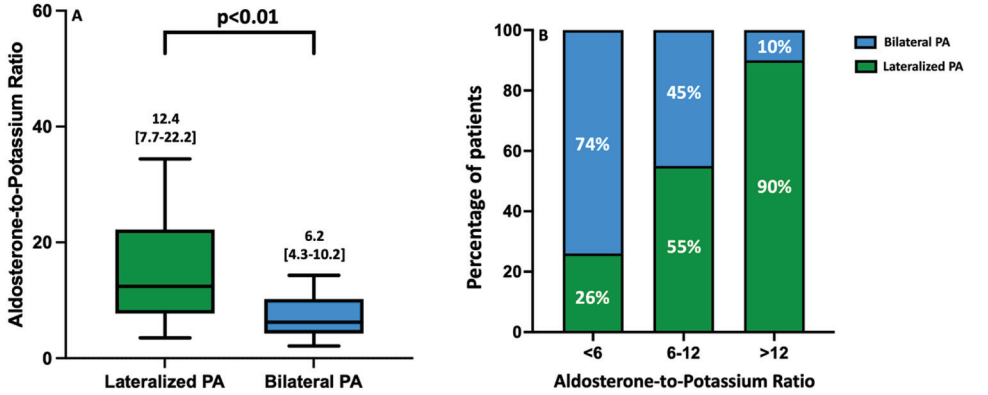

Figure 2. The aldosterone-to-potassium ratio and PA subtypes. (A) Box plots comparing APR between patients with lateralized and bilateral PA. Each box shows the median (solid line) and interquartile range (IQR), with whiskers extending to 1.5 times the IQR. Median values [IQR] are shown for each group. (B) Distribution of PA subtypes across three APR categories (<6, 6 to 12, and >12), illustrating the shift in subtype prevalence at different APR levels.

PA, primary aldosteronism; APR, aldosterone-to-potassium ratio

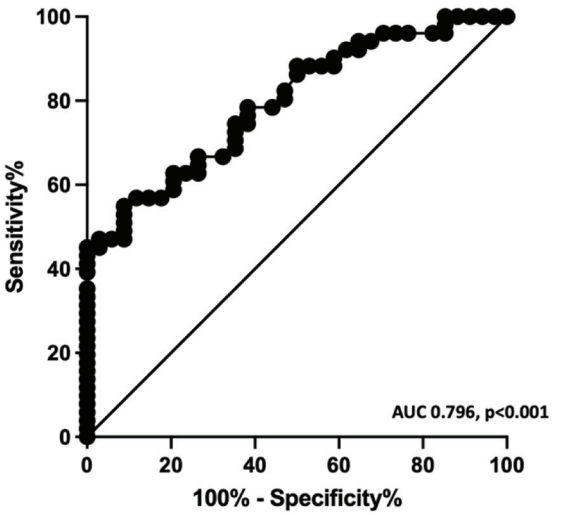

Figure 3. ROC curve of the aldosterone-to-potassium ratio (APR) for predicting lateralized PA.

ROC, receiver operating characteristic; AUC, area under the curve; PA, primary aldosteronism

Table 3. Postoperative outcomes of 43 patients with lateralized PA

Postoperative outcomes	n=43; n (%)
Clinical outcomes	
Complete	21 (49)
Partial	21 (49)
Absent	1 (2)
Biochemical outcomes (n=40)	
Complete	35 (88)
Partial	5 (12)
Absent	0 (0)

PA=primary aldosteronism

Discussion

The present study evaluated the performance of a simplified tool that uses APR to predict lateralized PA in patients with unilateral adrenal nodules in a Thai population. APR was selected because its components, PAC and serum potassium, are routinely measured during the diagnostic workup of PA and showed significant differences between patients with lateralized and bilateral PA. The findings support the potential clinical utility of APR, which demonstrated reasonable diagnostic performance and may help identify appropriate candidates for unilateral adrenalectomy, especially in settings where AVS is unavailable or yields inconclusive results.

Previous studies had evaluated APR for subtyping PA, with proposed cut-off values ranging from 12 to 15[26-28]. Puar et al.[26] investigated 103 patients with PA in Singapore and reported high diagnostic performance of APR (AUC 0.80, 95% CI 0.70 to 0.89), proposing a cut-off value of greater than 15 for lateralized PA. However, their criteria for defining lateralized PA were inconsistent, combining LI of 4 or more and LI 2 to 4 with subjective expert input, which may have introduced variability. Their findings were subsequently validated in the SPARTACUS trial[29] involving European populations, confirming APR as a reliable tool (AUC 0.73, 95% CI 0.62 to 0.83). A study from Turkey[28] proposed an APR cut-off of 12, similar to the present study findings, and applied consistent diagnostic criteria using LI of 4 or greater following cosyntropin stimulation. However, the sample size was small, with only 35 patients

included, which limited the generalizability of its results. A large study from Spain[27] involving 328 patients demonstrated a 90% probability of lateralized PA at APR values greater than 15. Nevertheless, methodological heterogeneity, including mixed AVS protocols and the inclusion of patients diagnosed postoperatively without AVS, may have affected the consistency of its conclusions.

The slightly lower APR threshold observed in the present study may reflect the characteristics of the cohort, which included patients more likely to have lateralized PA, particularly those with unilateral adrenal nodules. This imaging feature is commonly associated with APAs[17,30] and is included in several scoring systems designed to predict lateralized PA[31-33]. By focusing on this subgroup, a lower APR threshold may still provide comparable diagnostic performance. An additional advantage of limiting the analysis to this population is that, when the APR suggests lateralized PA, it also provides guidance on the surgical side. This contrasts with studies that included patients with bilateral adrenal lesions or normal adrenal imaging, in which lateralization prediction does not help determine the surgical side.

APAs, the main source of lateralized PA, are frequently associated with KCNJ5 driver mutations, particularly in Asian populations[34-37], including the Thai population[38]. These patients typically present with features such as markedly elevated aldosterone levels, profound hypokalemia[38-41], and the presence of large, well-visualized adrenal nodules on imaging[36,42-44]. Given these features, the APR may be especially effective in identifying lateralized PA in Asian patients with apparent adrenal nodules. However, since APA mutation profiles differ by ethnicity, further studies in diverse populations are needed to validate and generalize the utility of APR.

The present study has limitations. Potential contributors to hypokalemia, such as hypomagnesemia and gastrointestinal potassium loss, were not assessed. In addition, the presence of unilateral adrenal hyperplasia with a non-functioning contralateral adrenal nodule may compromise APR accuracy and lead to inappropriate surgical selection based on imaging findings. However, this condition is rare, accounting for only 1% to 5% of PA cases[10,45]. Adrenal CT findings in such cases can vary, showing normal glands, enlargement, or nodules. In two prior studies, all eight reported cases of unilateral adrenal hyperplasia with enlargement or small nodules on CT were concordant with the side of aldosterone excess identified by AVS[45,46]. Likewise, in the present study cohort, all patients with lateralized PA showed concordance between CT findings and AVS lateralization.

Conclusion

The APR offers a practical approach to predicting lateralized PA in patients with unilateral adrenal nodules. Its diagnostic performance supports its utility as a simplified alternative for subtype classification, particularly when AVS is unavailable.

What is already known about this topic?

AVS is the current standard for subtyping PA, but it is limited by accessibility and technical failure. The APR has been proposed as a simple clinical tool for subtyping PA, yet no standardized cut-off has been established, particularly in patients with unilateral adrenal nodules.

What does this study add?

In Thai patients with PA and unilateral adrenal nodules, the APR demonstrated good diagnostic performance (AUC 0.796) for predicting lateralized PA. A cut-off value above 12 is proposed, while a threshold above 14.5 may be used to maximize specificity.

Acknowledgement

The authors would like to express their sincere gratitude to all patients and healthcare personnel at Thammasat University Hospital for their participation and support in the present study.

Data availability

Individual-level data from the present study, with all personal identifiers removed, may be made available upon reasonable request. Interested researchers must provide a clearly defined study hypothesis and a detailed statistical analysis plan. Requests should be submitted to the corresponding author and will be evaluated by the study team. Data access will be granted based on the scientific value of the proposed research. A formal data use agreement will be required.

Funding disclosure

No funding was received for the present study.

Conflicts of interest

The authors declare no conflict of interest with the present work.

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