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The value of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red cell distribution width, and their combination in predicting acute pancreatitis severity

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Abstract. – OBJECTIVE: Acute pancreatitis is one of the most common causes of acute abdominal pain requiring hospitalization worldwide. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) are novel inflammatory markers that have been investigated in various diseases associated with an inflammatory response, achieving many positive results. Evaluating the NLR, PLR, RDW, and their combination to predict acute pancreatitis severity can help clinicians have an appropriate initial treatment strategy.

PATIENTS AND METHODS: This prospective cohort study enrolled 131 patients diagnosed with acute pancreatitis at Gia Dinh Hospital, Ho Chi Minh City, between December 2021 and August 2022. Patients with the following features were excluded from our study: age < 18 years old, time from symptom onset to admission of > 72 hours; patients with autoimmune disease, decompensated cirrhosis, active tuberculosis, heart failure (New York Heart Association class 4), end-stage renal failure, pregnancy, active severe acute respiratory syndrome coronavirus 2 infection, and chronic pancreatitis.

RESULTS: There were 21 severe acute pancreatitis (SAP) cases (16%). The area under the receiver operating characteristic curve for predicting SAP was 0.82 for NLR, 0.72 for PLR, and 0.73 for RDW. When the cutoffs of 13.5 for NLR, 202.7 for PLR, and 13.1% for the RDW were used, the negative predictive values in predicting SAP were 93.1%, 91.9%, and 98.8%, respectively. This finding demonstrates the value of inflammatory markers in predicting SAP. The combination of these markers did not show an advantage in predicting SAP compared to the single markers.

CONCLUSIONS: High NLR, PLR, and RDW are associated with SAP. These indices are good indicators for predicting SAP. In our study, the combination of inflammatory markers did not improve SAP prediction compared to the individual markers.

Key Words:
Acute pancreatitis, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Red cell distribution width.

Introduction

Acute pancreatitis (AP) is one of the most common causes of acute abdominal pain requiring hospitalization worldwide. Data suggests that 20-30% of patients with AP develop severe AP (SAP)[1], with the mortality rate ranging from 13% to 35%[1]. Therefore, early detection of severe cases is crucial to identify patients needing more aggressive management.

The 2012 Modified Atlanta Classification divides AP into mild, moderate-severe, and severe[2]. Many scoring systems have been proposed and accepted to evaluate AP severity, such as the Ranson criteria, the Acute Physiology and Chronic Health Evaluation II system, Bedside Index for Severity in AP (BISAP) score, and the Glasgow scale[3]. However, the complexity and time required to determine the parameters in these systems make them more inappropriate in clinical settings.

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) are novel inflammatory markers that can be easily assessed from the complete blood count. These indices have been studied in various conditions associated with inflammatory responses, such as cardiovascular disease and cancer, achieving many positive results[4,5]. Many studies[6,7] have shown that the

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NLR, PLR, and RDW can predict AP severity with high precision[6,7]. A retrospective case-control study[8] found that the RDW was the primary predictor of SAP. Another study[9] investigated the predictive values of the NLR as an indicator of SAP in emergency department patients, finding it a useful prognostic factor. However, only one study[10] has examined the relationships of the NLR and PLR with AP severity in Vietnam.

This study aims to determine the value of these markers as early indicators of AP severity according to the Modified Atlanta Classification 2012. Its results can be applied in clinical settings, helping to identify SAP cases needing more intensive care.

Patients and Methods

Participants

This prospective cohort study consecutively enrolled patients with AP admitted to Gia Dinh Hospital, Ho Chi Minh City, between December 2021 and August 2022.

AP was diagnosed and classified according to the 2012 revision of the Atlanta Classification and definitions by the international consensus[2]. The AP diagnosis requires at least two of these features: abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); serum lipase and/or amylase ≥ 3 times greater than the upper limit of normal; characteristic AP findings on abdominal ultrasound, computed tomography (CT), and/or magnetic resonance imaging (MRI)[2]. Mild AP (MAP) was defined as an absence of organ failure and an absence of local or systemic complications. Moderately severe AP (MSAP) was defined as no evidence of persistent organ failure but the presence of local or systemic complications and/or organ failure that resolved within 48 hours. SAP was defined as persistent organ failure (> 48 hours)[2]. Patients with the following features were excluded from our study: age < 18 years old, time from symptom onset to admission of > 72 hours; patients with autoimmune disease, decompensated cirrhosis, active tuberculosis, heart failure (New York Heart Association class 4), end-stage renal failure, pregnancy, active severe acute respiratory syndrome coronavirus 2 infection, and chronic pancreatitis (Figure 1).

The demographics of all enrolled patients were recorded at admission. Vital signs (blood pressure, respiratory rate, and pulse rate) and laboratory parameters [white blood cell count (WBC), neutrophil count, lymphocyte count, hemoglobin level, platelet level, RDW, hematocrit (HCT), renal function, amylase/lipase, triglyceride, calcium, and arterial blood gas] were also recorded. The NLR and PLR are the ratios of the absolute neutrophil or platelet counts to the lymphocyte count, respectively. Patients with AP were followed up for outcome measurement. All patients were classified into two groups: SAP and non-SAP (MAP and MSAP). The dependent variables other than AP severity included intensive care unit (ICU) admission, hospital stay length, local complication, cardiovascular complication, respiratory failure, renal failure, multiple organ dysfunction, persistent organ failure (≥ 48 hours), and death.

Ethical Approvals

Our study was approved by the Institutional Review Board and Medical Ethics Committee of Pham Ngoc Thach University of Medicine (approval number: 556/TĐHYKPNT-HĐĐĐ; approval date: December 14, 2021).

Statistical Analysis

The continuous variables are expressed as mean ± standard deviation (SD) or median (range) and were compared between the two groups using the independent sample *t*-test, the Mann-Whitney U test, or Fisher's exact test (when sample sizes were very small). The categorical variables are expressed as number (percentage) and were compared between the two groups using the χ^2 test. The accuracy of each marker in predicting AP severity was assessed using receiver operating characteristic (ROC) curves. Combination models were developed using binary logistic regression. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 20.0, (IBM Corp., Armonk, NY, USA) (Figure 1).

Results

This study enrolled 131 patients with AP, of which 19 (14.5%) were classified as MAP, 91 (69.5%) were classified as MSAP, and 21 (16.0%) were classified as SAP. Tables I and II show the patients' baseline characteristics. Figures 2 and 3 show the imaging characteristics of necrotizing AP in our study. The mortality rate was 4.6% in the study cohort and 27.3% in the SAP group. The median age was significantly higher in the SAP group (p = 0.028). Furthermore, the proportion of ICU admissions and hospital stay lengths

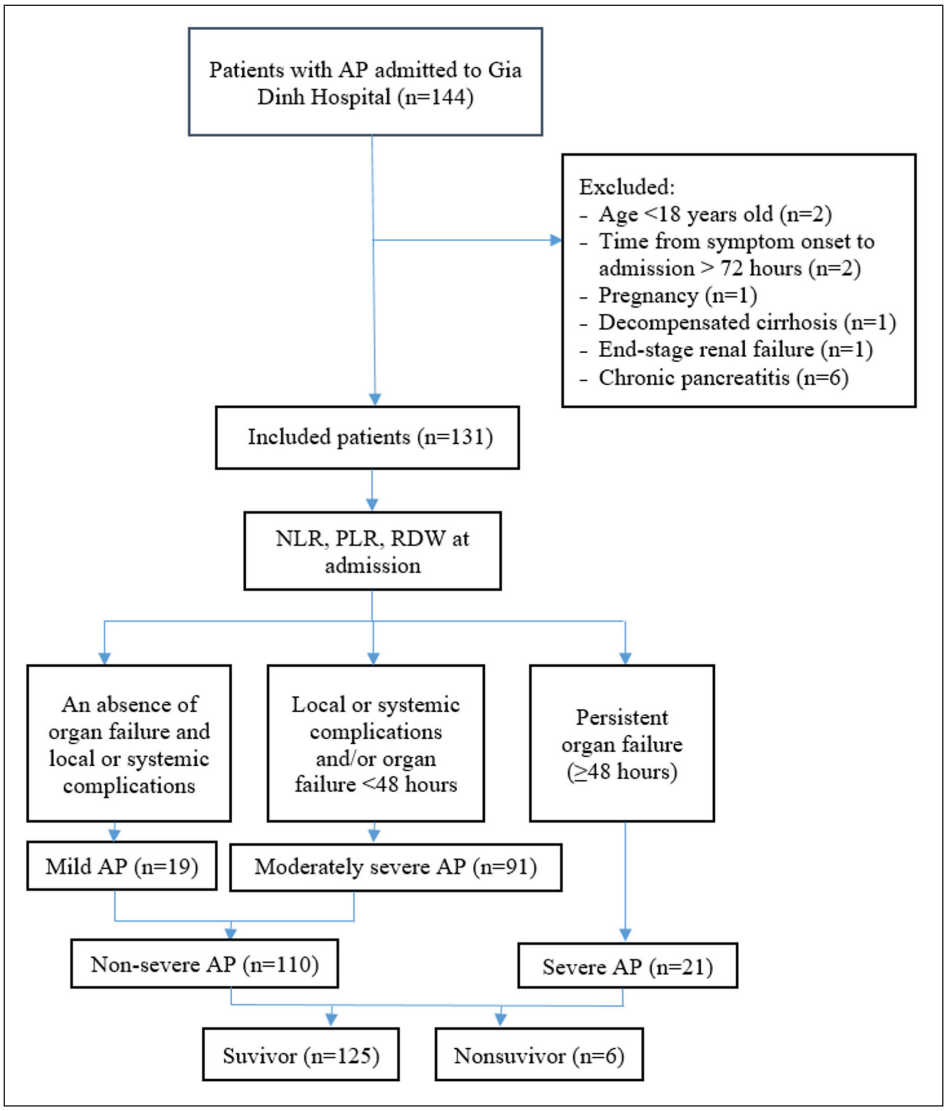

Figure 1. Flow diagram of study.

differed significantly between the SAP and non-SAP groups. The SAP group was more likely to develop local and systemic complications and persistent organ failure. Our study found no relationship between AP severity and sex, body mass index (BMI), or etiology.

The NLR, PLR, RDW, WBC, neutrophil count, and lymphocyte count were significantly higher in the SAP group than in the non-SAP group ($p < 0.05$). The platelet count, HCT level, amylase level, and triglyceride level did not differ significantly between the SAP and non-SAP groups.

Tables III and IV show the area under the ROC (AUC) analysis, optimal cutoff, sensitivity, specificity, positive predictive value, and negative predictive value for the NLR, PLR, RDW, and their combination in predicting SAP. Among these inflammation markers, the NLR showed good predictive ability for AP severity (AUC = 0.82, $p < 0.001$), while the PLR (AUC = 0.72, $p = 0.001$) and RDW (AUC = 0.73, $p = 0.001$) showed fair predictive ability for AP severity (Figure 4). However, no significant pairwise differences existed between the NLR, PLR, and RDW: NLR *vs.* PLR ($p = 0.166$), NLR *vs.* RDW ($p = 0.212$), and RDW *vs.* PLR ($p = 0.906$). The NLR had the highest specificity (85.5%), and RDW had the best sensitivity (76.2%). All three makers had good negative predictive values (> 90%).

Among the combinations of inflammatory markers, the NLR+PLR combination had the highest AUC (0.83). However, no significant pairwise differences existed between the NLR+PLR, PLR+RDW, NLR+RDW, and NLR+PLR+RDW combinations (Figure 5). Moreover, none of the

Table I. Demographic data of the study participants.

	SAP (*n* = 21)	Non-SAP (*n* = 110)	*p*	Total
Age (years), median (range)	55.6 (44 - 66)	43.0 (34 - 3)	0.028*	46 (36 - 61)
Sex, *n* (%)			0.518	
Male	13 (61.9%)	76 (69.1%)		89 (67.9%)
Female	8 (38.1%)	34 (30.9%)		42 (32.1%)
BMI (kg/m^2), mean ± SD	23.2 ± 0.9	23.4 ± 0.3	0.839	23.3 ± 3.6
Etiology, n (%)				
Alcohol	7 (33.3%)	46 (41.8%)	0.516	53 (40.5%)
Gallstones	4 (19.0%)	26 (23.6%)	0.468	30 (22.9%)
Hypertriglyceridemia	6 (28.6%)	11 (10.0%)	0.032**	17 (13.0%)
Alcohol + hypertriglyceridemia	2 (9.5%)	13 (11.8%)	1.000**	15 (11.5%)
Other	2 (9.5%)	14 (12.7%)	1.000**	16 (12.1%)
ICU admission, n (%)	16 (76.2%)	0 (0%)	< 0.001*	16 (12.2%)
Hospital stay length (days), median (range)	11 (6 - 20)	6 (4 - 7)	< 0.001*	6 (4 - 9)
Local complication, n (%)	21 (100%)	84 (76.4%)	0.013*	105 (80.2%)
Systemic complication, n (%)	5 (23.8%)	1 (0.9%)	< 0.001*	6 (4.6%)
Persistent organ failure, n (%)				
Renal failure	10 (47.6%)	0 (0)	< 0.001*	10 (7.6%)
Respiratory failure	17 (81.0%)	0 (0)	< 0.001*	17 (13.0%)
Cardiovascular failure	7 (33.3%)	0 (0)	< 0.001*	7 (5.3%)
Death, n (%)	6 (28.6%)	0 (0)	< 0.001*	6 (4.6%)

SAP, severe acute pancreatitis; BMI, body mass index; ICU, intensive care unit; *, Mann-Whitney U test; **, Fisher's exact test.

four combinations differed significantly from the single markers ($p > 0.05$).

Discussion

AP is an acute inflammatory disease characterized by the activation of both innate and adaptive immune systems, with mortality primarily occurring due to organ failure[11]. In our study, high NLR, PLR, and RDW were associated with SAP, of which NLR was the strongest predictor of SAP (AUC = 0.82), although the predictive abilities of the three inflammatory markers did not differ significantly. Combining these markers did not improve predictions compared to the individual markers.

Table II. Laboratory findings of patients with AP.

	SAP (*n* = 21)	Non-SAP (*n* = 110)	*p*	Total
WBC (K/µL)	17.0 ± 1.3	14.1 ± 0.4	0.010	14.5 ± 4.7
Neutrophil (K/µL)	14.8 ± 1.1	11.3 ± 0.4	0.001	11.9 ± 4.6
Lymphocyte (K/µL)	0.8 (0.6 - 1.2)	1.6 (1.2 - 2.1)	< 0.001*	1.5 (1.0 - 2.0)
Platelet (G/L)	220.1 ± 17.7	252.6 ± 6.8	0.063	247 ± 73.4
HCT (%)	42.7 ± 1.4	43.0 ± 0.5	0.855	43.0 ± 5.6
Amylase (U/L)	695.9 (321.6 - 1,202.5)	487 (186.5 - 1,177.3)	0.380*	519.5 (189.0 - 1,199.5)
Triglyceride (mmol/L)	3.3 (1.5 - 56.7)	3.8 (1.2 - 13.8)	0.337*	3.5 (1.2 - 15.7)
NLR	15.0 (10.6 - 23.1)	6.9 (4.1 - 11.1)	< 0.001*	7.8 (5.2 - 13.1)
PLR	224.6 (166.3 - 351.6)	159.9 (109.3 - 212.4)	0.001*	172.6 (113.9 - 231.4)
RDW (%)	13.5 (13.1 - 13.8)	12.7 (12.3 - 13.4)	0.001*	12.9 (12.4 - 13.5)

SAP, severe acute pancreatitis; WBC, white blood cell count; HCT, hematocrit; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; *, Mann-Whitney U test.

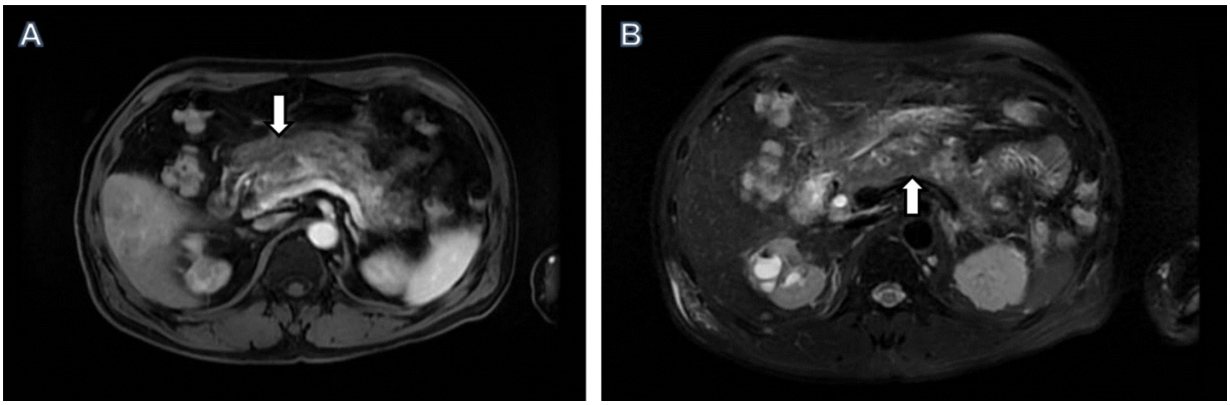

Figure 2. A-B, MRI images of a 53-year-old patient with necrotizing AP *(arrow)*.

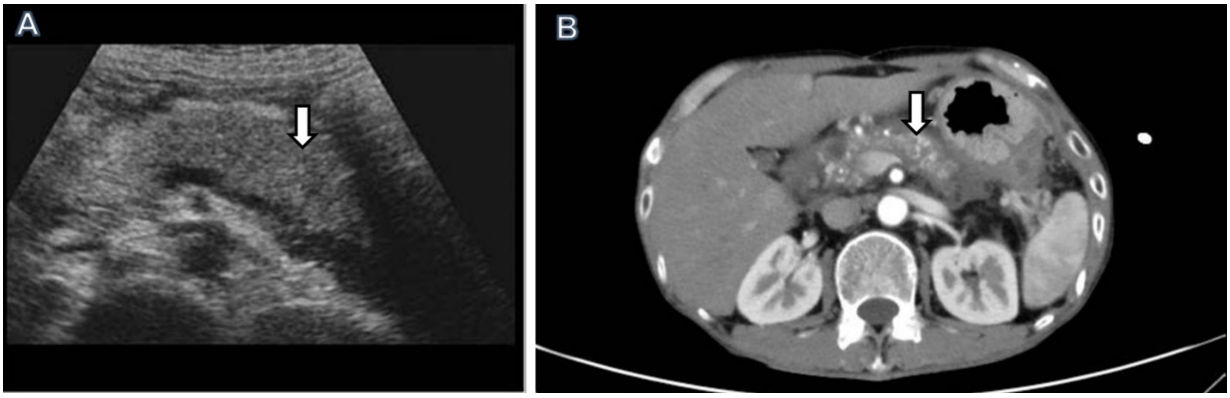

Figure 3. Ultrasound (**A**) and CT (**B**) images showing parenchymal pancreatic necrosis *(arrow)* in a 65-year-old patient.

Table III. Comparison of ROC curves for inflammation markers in predicting SAP.

Factors	AUC (95% CI)	*p*	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	0.82 (0.74 - 0.91)	< 0.001	13.5	66.7	85.5	46.7	93.1
PLR	0.72 (0.60 - 0.84)	0.001	202.7	66.7	71.8	31.1	91.9
RDW	0.73 (0.62 - 0.84)	0.001	13.1	76.2	69.1	32.0	93.8

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width.

Table IV. Comparison of ROC curves for inflammation marker combinations in predicting SAP.

Factors	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR+PLR	0.83 (0.74 - 0.91)	61.9	87.3	48.2	92.3
PLR+RDW	0.76 (0.73 - 0.90)	57.1	91.8	57.1	91.8
NLR+RDW	0.82 (0.66 - 0.86)	52.4	92.7	57.9	91.1
NLR+PLR+RDW	0.82 (0.73 - 0.90)	47.6	96.4	73.3	91.4

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width.

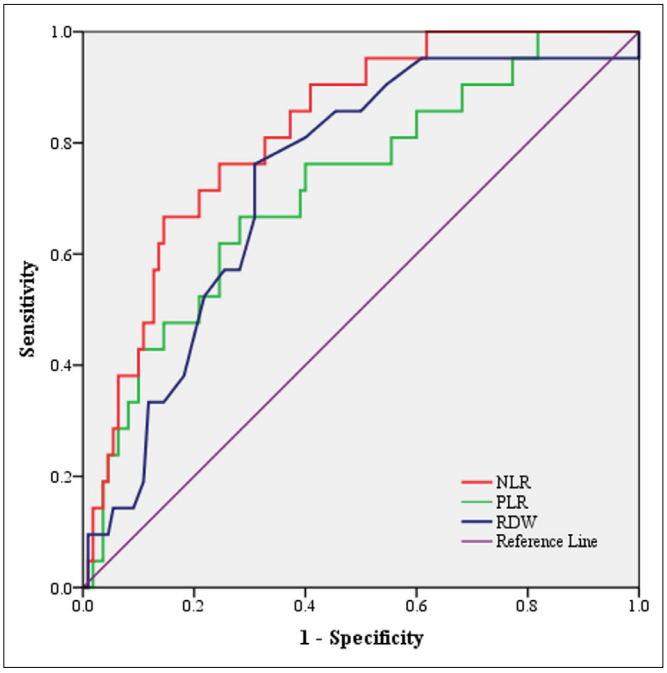

Figure 4. Comparison of the ROC curves for the NLR, PLR, and RDW in predicting SAP. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width.

Lymphocytes are an important type of white blood cell. Some studies[12] have shown a correlation between low lymphocyte levels and AP severity. Systemic inflammatory response syndrome is characterized by increased neutrophil and decreased lymphocyte counts, reflecting significant changes in the immune system[4]. This phenomenon occurs because the apoptosis of neutrophils is delayed, leading to an increase in leukocytes and neutrophils, which aggravates inflammation. The NLR represents the balance between inflammatory activation (neutrophils) and inflammation regulation (lymphocytes). The higher its value, the more imbalanced the inflammatory state[13].

Numerous studies[6-9] have examined the association between the NLR and SAP. A Mumbai-based study by Junare et al[7] demonstrated that the NLR had an excellent ability to predict ICU admission (AUC = 0.943) and organ failure (AUC = 0.940). Park et al[9] found that the NLR had high sensitiv-

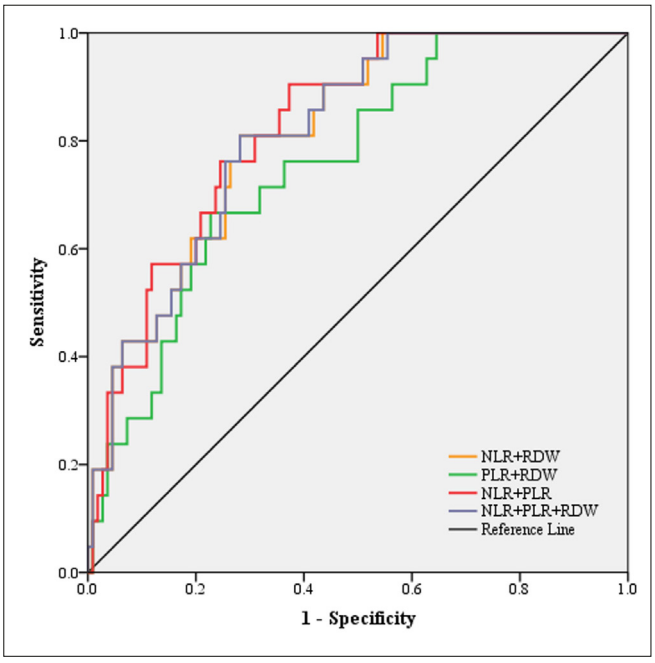

Figure 5. Comparison of the ROC curves for inflammation marker combinations in predicting SAP. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width.

ity (82.7%) and specificity (70%); with an optimal cutoff for the baseline NLR of 8.6, it had a better AUC than the C-reactive protein (CRP), creatinine, blood urea nitrogen, and WBC. In 2019, Zhou et al[6] studied 406 patients with AP, finding that a cutoff for the NLR of 10.3 predicted SAP with a sensitivity of 64.0%, specificity of 77.0%, positive predictive value of 31.0%, and negative predictive value of 93.1%. In our study, we found that the best cutoff for the NLR was 13.5, providing a sensitivity of 66.7%, specificity of 85.5%, positive predictive value of 46.7%, and negative predictive value of 93.1%. The high specificity and negative predictive value show that the NLR is valuable in identifying and excluding the severe progression risk of AP. Our results are consistent with the literature. The higher cutoff in our study may be due to a difference in sampling method, etiologies, and diversity in NLRs between populations.

The PLR has been shown to be an indicator of severity and predictive in some diseases, including AP[14]. Takeyama et al[15] demonstrated that impaired cellular immunity due to peripheral lymphocyte apoptosis is associated with developing subsequent infectious complications in AP. Studies[16,17] have shown that platelets play an important role in immune regulation and the inflammatory response. Our study found that the PLR had an optimal cutoff of 202.7 to predict AP severity, providing an AUC of 0.72, sensitivity of 66.7%, specificity of 71.8%, positive predicting value of 31.1%, and negative predicting value of 91.9%. As well as NLR, with a high negative predicting value, PLR is likely a reasonable predictive parameter of non-severe AP. The results of our study are inconsistent with some literature. Junare et al[7] found that the PLR had a good ability to predict ICU admission and organ failure. Conversely, Zhou et al[6] reported that the AUC for the PLR in predicting SAP was only 0.62. We have not yet been able to explain this difference.

The RDW is a quantitative measure of the variability in the size of circulating erythrocytes[18]. When calculating the AUC for the SAP outcome, we found that the AUC of the RDW was 0.73, indicating that it is an inflammatory marker of moderate value. This result was similar to Zhou et al[6] (AUC = 0.79) but lower than Gravito-Soares et al[8] (AUC = 0.96). Different studies, including ours, have reported relatively similar cutoffs for the RDW in predicting SAP. Zhou et al[6], Gravito-Soares et al[8] and our study suggested an RDW cutoff of 13.4%[6], 13.1%[8], and 13.1%, respectively. Zhou et al[6] reported that the RDW was significantly higher in the SAP group than in the non-SAP group and was a useful predictive parameter for AP severity at the early admission stage, with a sensitivity of 78.6% and a negative predictive value of 94.9%[6]. Gravito-Soares et al[8] concluded that the RDW was an excellent predictor of severity and superior to prognostic scores, such as the Ranson, BISAP, and Modified Marshall[8]. These results show that the RDW has good sensitivity in predicting SAP (> 70%) and a high negative predictive value (> 90%). Our results are similar to the literature; the RDW, NLR, and PLR were strong and positive makers in identifying patients less likely to have SAP. Therefore, NLR, PLR, and RDW are easily obtained, inexpensive, noninvasive serum markers that should be widely used in practice.

Our study shows that combining the NLR, PLR, and RDW pairwise or triple-wise provided AUCs of > 0.8 in predicting SAP, except for PLR+RDW (AUC = 0.76). Therefore, combining these markers did not improve SAP prediction compared to the individual markers.

Limitations

Some potential limitations of this study should be noted. Firstly, the small number of patients in the SAP group might have impacted the results. Therefore, a larger prospective study is needed to validate our results. Secondly, our study did not routinely use CT scans, which might have led to misdiagnoses in some cases.

Conclusions

Increased NLR, PLR, and RDW were associated with SAP. The NLR, PLR, and RDW at admission were suitable as reliable markers to exclude SAP with good predicting values. Combining these inflammatory markers did not improve SA prediction. Therefore, combining them is not necessary for predicting SAP in clinical practice.

Ethics Approval

Our study was approved by the Institutional Review Board and Medical Ethics Committee of Pham Ngoc Thach University of Medicine (approval number: 556/TĐHYK-PNT-HĐĐĐ; approval date: December 14, 2021).

Informed Consent

Informed consent was obtained from all participants.

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

Authors' Contributions
Study concept and design: Vo Hieu Hanh, Truong-Thi Ngoc Nhu, and Nguyen Minh Duc; acquisition of data: Vo Hieu Hanh, Truong-Thi Ngoc Nhu, and Nguyen Minh Duc; analysis and interpretation of data: Vo Hieu Hanh, Truong-Thi Ngoc Nhu, Ho-Thi Hoa Binh, Vo Hong Minh Cong, Tran-Thi Khanh Tuong, and Nguyen Minh Duc; drafting of the manuscript: Vo Hieu Hanh, Truong-Thi Ngoc Nhu, and Nguyen Minh Duc; critical revision of the manuscript: Vo Hieu Hanh, Truong-Thi Ngoc Nhu, and Nguyen Minh Duc; study supervision: Vo Hieu Hanh and Vo Hong Minh Cong confirm the authenticity of all the raw data. All authors read and approved the final version of this manuscript.

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Conflicts of Interest
There are no conflicts of interest to declare.

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