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ORIGINAL ARTICLE

The early prognostic value of inflammatory markers in patients with acute pancreatitis

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KEYWORDS
Acute pancreatitis;
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Summary
Objectives: The aim of this study was to compare the prognostic value of inflammation-based prognostic markers with the more mature scoring system BISAP in patients with AP and identify the best predictors.
Patients and methods: We retrospectively analysed the data of patients with AP who were treated in our hospital from January 2017 to March 2018 and compared the prognostic value of these inflammation-based prognostic markers with the BISAP score in patients with AP.
Results: Higher BISAP score, NLR, PLR, ACC, and BUN gradually increased (all $P < 0.05$), and lower LMR and TC ($P < 0.001$) were associated with severity of AP. Compared with the patients without persistent organ failure, the patients with POF were older ($P = 0.049$) and had a higher BISAP score ($P < 0.001$), NLR ($P = 0.003$), PLR ($P < 0.001$) and ACC ($P = 0.047$), BUN ($P = 0.011$), and creatinine ($P = 0.023$), RDW ($P = 0.021$), but lower LMR ($P = 0.003$) and TC ($P < 0.001$) at baseline. The BISAP score (OR = 2.117, 95% CI 1.487 to 3.016, $P < 0.001$), NLR (OR = 1.053, 95% CI: 1.009 to 1.101, $P = 0.019$) and TC (OR = 0.088, 95% CI: 0.024 to 1.030, $P < 0.001$) were independent factors for predicting SAP. For predicting the occurrence of POF, TC and PLR had an area under the ROC curve (TC AUC = 0.784, $P < 0.001$, with a 2.18 cut-off value, PLR AUC = 0.731, $P < 0.001$, with a 173.13 cut-off value) that was not inferior to the BISAP score (AUC = 0.708), and PLR had the best sensitivity (95.8%), BUN had the best specificity (44.71%), respectively. There is no difference in their predictive value for POF.
Conclusions: NLR and TC are the most powerful markers in this patient series, they have a prognostic value which is not weaker than BISAP, and are equally simple, rapid.

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Introduction

Acute pancreatitis (AP) is an acute inflammatory process that starts with local acinar cell injury with variable involvement of other regional tissues or remote organ systems [1]. Although the majority of acute pancreatitis cases are mild, and the prognosis is good, there are still 20—30% of patients who experience serious complications, such as necrosis or organ failure. The overall mortality rate of AP is 5—10% [2]. Therefore, to reduce the risk of early death and to develop early interventions to reduce mortality, clinicians should identify the severity of AP and the presence of complications early.

Currently, most classical methods for assessing the severity of acute pancreatitis have some limitations—namely, most of these methods are not simple, rapid and economical enough. The Ranson [3] and modified Glasgow score [4] require data that were not routinely collected at the time of hospitalization, and both need more time to complete. The APACHE-II was originally developed as an intensive care instrument and requires the collection of several parameters, some of which may not be relevant to AP prognosis [5]. Through these scoring systems, it is currently not possible to judge the severity of AP early, and some patients are not diagnosed within the optimal time frame for early diagnosis and treatment. The BISAP (bedside index for severity in AP) is a simple and accurate method for the early identification of AP patients at increased risk for in-hospital mortality [6]. C-reactive protein, IL-6 also have been used for predicting the severity of pancreatitis [7,8]. In recent research, in the secondary care hospital, where most patients with AP were initially admitted, compared to the interleukin-6, C-reactive protein, procalcitonin, D-dimer and soluble fms-like tyrosine kinase-1, uPAR measurements had the same value in this prediction [9]. But these simple methods do not make clinicians feel comprehensive and simple. When acute pancreatitis occurs, trypsin is released and the pancreatic exocrine function is activated, which in turn destroys the mechanism of pancreatic self-defense and aggravates the damage and destruction of pancreatic cells [10]. As a result, vascular endothelium is damaged, motor dystonia, vascular permeability are increased, more leukocyte migrate to tissues, and coagulation systems are activated [11]. So a lot of inflammatory markers based on blood cell changes that were inexpensive and easily obtained during the early stage of hospitalization were used to assess the severity of AP, such as the red cell distribution width (RDW) [12], neutrophil—lymphocyte ratio (NLR), lymphocyte—monocyte ratio (LMR) [13], platelet lymphocyte ratio (PLR) [14], total calcium (TC) and albumin-corrected calcium (ACC) [15] and blood urea nitrogen (BUN) [16]. However, there is few literature which has a comprehensive comparison of their predictive functions.

In this study, we retrospectively analysed the data of patients with AP who were treated in our hospital from January 2017 to March 2018 and compared the prognostic value of these inflammation-based prognostic markers with the relatively mature scoring system BISAP in patients with AP to identify the best predictors.

Patients and methods

Participants

This retrospective cohort analysis consecutively enrolled a series of patients with AP who were admitted to the Department of Pancreatic Surgery at our hospital between 1 March 2017 and 1 April 2018. A diagnosis of AP required two of three features:

- prolonged abdominal pain characteristic of AP;
- threefold elevation of serum amylase and/or lipase levels above the normal range;
- characteristic findings of AP on abdominal MRI and/or CT scan.

Patients with the following features were excluded from this group:

- patients who had received treatment before admission;
- patients who had tumours;
- patients who had a history of pregnancy;
- patients who had an immune disease.

Acute pancreatitis was categorized into mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) in accordance with the revised Atlanta classification [17]. Consequently, MAP was considered to be associated with AP clinical and biochemical changes, no organ failure or local or systemic complications. MSAP has clinical and biochemical changes of AP accompanied by transient organ failure (less than 48 h) or local or systemic complications without persistent organ failure (cannot be recovered in 48 h). Local complications included acute peripancreatic fluid collection, pancreatic pseudocysts, acute necrotic collection, and walled-off necrosis. Exacerbation of pre-existing comorbidities, such as coronary artery disease or chronic lung disease, precipitated by acute pancreatitis was defined as a systemic complication. SAP was considered to be the presence of persistent (over 48 h) organ failure (POF) (respiratory system, cardiovascular or renal failure that cannot be recovered; one or more organs may be involved). Organ failure included shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency (arterial PO_2 < 60 mmHg at room air or the need for mechanical ventilation), or renal failure (serum creatinine level > 2 mg/dL after rehydration or haemodialysis) [18,19]. The NLR, PLR and LMR were computed by calculating the ratio of the absolute neutrophil, monocyte, platelet and lymphocyte counts. The analysis was conducted using the values on the day of hospitalization before any treatment. RDW, TC, ACC were also collected, except for the blood urea nitrogen and creatinine, which were assessed according to the values after 48 hours.

The BISAP score was assessed on the day of admission. We calculate the scores according to the following criteria:

- ages (> 60 years);
- blood urea nitrogen (BUN) (> 25 mg/dL);
- pleural effusion (on chest radiography or CT);

Table 1 Comparison of baseline characteristics among the patients with different severities.

Variables	MAP	MSAP	SAP	*P*	Statistic
Age (y)	52.38 ± 18.05	52.43 ± 16.66	61.17 ± 15.73	0.193	$\chi^2 = 3.289$
Sex (male)	79 (60.8%)	84 (64.1%)	11 (61.1%)	0.850	$\chi^2 = 0.325$
Aetiology (1/2/3/4)%	62.3%/18.5%/6.9%/12.3%	47.3%/35.1%/4.6%/12.8%	50%/16.7%/0%/33.3%	0.013	$\chi^2 = 15.340$
Accompanied by liver failure	25 (19.2%)	26 (19.8%)	2 (11.1%)	0.759	$\chi^2 = 0.586$
Accompanied by diabetes	16 (12.3%)	28 (21.4%)	1 (5.6%)	0.057	$\chi^2 = 5.555$
BISAP	0.792 ± 0.814	1.519 ± 0.931	2.111 ± 0.676	0.000	$\chi^2 = 54.920$
NLR	8.344 ± 0.732	15.256 ± 0.998	20.636 ± 3.207	0.000	$\chi^2 = 54.089$
PLR	192.247 ± 9.974	256.889 ± 13.791	322.299 ± 38.471	0.000	$\chi^2 = 23.645$
LMR	2.537 ± 0.139	1.744 ± 0.109	1.331 ± 0.223	0.000	$\chi^2 = 32.017$
RDW (%)	12.946 ± 0.098	13.031 ± 0.107	13.500 ± 0.202	0.162	$\chi^2 = 1.831$
TC (mmol/L)	2.234 ± 0.014	2.155 ± 0.019	1.851 ± 0.081	0.000	$\chi^2 = 28.768$
ACC (mmol/L)	2.156 ± 0.248	2.233 ± 0.030	2.358 ± 0.115	0.020	F = 3.969
BUN (mmol/L)	5.301 ± 0.206	5.934 ± 0.270	9.956 ± 1.961	0.001	$\chi^2 = 13.545$
Creatinine (μmol/L)	67.615 ± 3.470	67.901 ± 3.353	118.389 ± 29.852	0.196	$\chi^2 = 3.261$
BUN/creatinine	0.145 ± 0.061	0.123 ± 0.030	0.105 ± 0.012	0.119	$\chi^2 = 4.252$

Continuous variables are presented as the mean ± SD.
Aetiology (1/2/3/4)%: 1, 2, 3 and 4 represent gallstones, hypertriglyceridaemia, alcohol and other aetiologies, respectively.
MAP: mild acute pancreatitis; MSAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; BISAP: bedside index for severity in AP; RDW: red cell distribution width; NLR: neutrophil—lymphocyte ratio; LMR: lymphocyte—monocyte ratio; PLR: platelet lymphocyte ratio; TC: total calcium; ACC: albumin-corrected calcium; BUN: blood urea nitrogen.

- the systemic inflammatory response syndrome (SIRS) defined by the presence of > 2 of the following criteria:
  - pulse: 90 beats/min,
  - respirations: 20/min or $PaCO_2$, 32 mmHg,
  - temperature: 38 °C or, 36 °C,
  - WBC count (> 12,000 or < 4000 cells/mm^3);
- altered mental status: defined as any record of disorientation, lethargy somnolence, coma or stupor in the medical record.

In the above five items, if there is one item within 24 hours scored 1 point, the total score is 5.

Patients with recurrent pancreatitis were enrolled only at first admission. For prognostic information, we focused on the severity of the disease. All clinical data were retrieved from medical records. We assessed the prognostic value of general inflammation-based prognostic markers (BISAP, NLR, PLR, LMR, RDW, TC, ACC and BUN) for predicting the severity of AP.

Ethics statement

Each patient was treated in accordance with the ethical principles outlined in the Declaration of Helsinki. Demographic information, including age, sex, aetiology and complications, and laboratory analysis was collected from medical records.

Statistical analysis

Variables are expressed as the mean ± SD or median (range) and categorical data as percentages, as appropriate. Differences between the groups were assessed using an independent sample *t*-test, Mann—Whitney U test or Chi^2 test, as appropriate. Multiple comparisons were performed by one-way analysis of variance or Kruskal—Wallis H tests, as appropriate. Multivariate logistic regression analyses were used to assess whether the inflammatory markers were independent factors for predicting SAP in patients with AP by unadjusted and adjusted models successively. The accuracy of each marker to predict the occurrence of organ failure was assessed using receiver operating characteristic (ROC) curves. The comparison of the AUC between BISAP scores and inflammatory markers was assessed by Hanley and McNeil. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 25.0 and MedCalc 18.5.

Result

Patient characteristics

A total of 279 patients with AP (130 MAP, 131 MSAP and 18 SAP) were enrolled in the study. Forty-one patients were excluded from the analysis. Twenty-seven patients received treatment before admission, eight patients had tumours, five patients suffered from postpartum pancreatitis, and one patient had immune disease. Tables 1 and 2 show the baseline characteristics of the patients. There were no significant differences in age ($P = 0.193$), sex ($P = 0.850$), accompanying liver failure or diabetes ($P = 0.759$, $P = 0.057$), RDW ($P = 0.162$), creatinine ($P = 0.196$), or BUN/creatinine ($P = 0.119$) among the three groups (MAP, MSAP and SAP). As the illness worsened, the BISAP score, NLR, PLR, ACC, and BUN gradually increased (all $P < 0.05$; Table 1), but the LMR and TC decreased ($P < 0.001$). Compared with the patients without POF, the patients with POF were older ($P = 0.049$) and had a higher BISAP score ($P < 0.001$), NLR ($P = 0.003$), PLR ($P < 0.001$) and ACC ($P = 0.047$), BUN ($P = 0.011$), and creatinine ($P = 0.023$), RDW ($P = 0.021$). Conversely, the LMR

Table 2 Comparison of baseline characteristics between the patients with and those without POF.

Variables	Patients accompanied with POF	Patients not accompanied with POF	*P*-value	Statistic
Age (y)	59.625 ± 3.585	52.345 ± 1.078	0.049	$t = 1.977$
Sex (male)	16 (66.7%)	158 (62.0%)	0.670	$\chi^2 = 0.207$
Accompanied by liver failure	5 (20.8%)	48 (18.8%)	0.810	$\chi^2 = 0.058$
Accompanied by diabetes	1 (41.7%)	44 (17.3%)	0.169	$\chi^2 = 3.661$
BISAP	1.917 ± 0.199	1.153 ± 0.058	0.000	$t = 3.820$
NLR	18.831 ± 2.799	11.776 ± 0.659	0.003	$Z = -2.998$
PLR	328.835 ± 31.862	221.780 ± 8.770	0.000	$Z = -3.747$
LMR	1.376 ± 0.193	2.154 ± 0.093	0.003	$Z = -2.924$
RDW (%)	13.542 ± 0.241	12.972 ± 0.712	0.021	$t = 2.323$
TC (mmol/L)	1.911 ± 0.068	2.197 ± 0.012	0.000	$Z = -4.599$
ACC (mmol/L)	2.374 ± 0.086	2.189 ± 0.020	0.047	$t = 2.091$
BUN (mmol/L)	8.822 ± 1.553	5.623 ± 0.172	0.011	$Z = -2.554$
Creatinine (μmol/L)	106.542 ± 22.656	67.682 ± 2.453	0.023	$Z = -2.274$
BUN/creatinine	0.097 ± 0.010	0.136 ± 0.035	0.629	$Z = -0.483$
Aetiology (1/2/3/4)%	54.2%/12.5%/8.3%/25%	54.5%/27.5%/5.1%/12.9%	0.155	$\chi^2 = 4.912$

Continuous variables are presented as the mean ± SD.
Aetiology (1/2/3/4)%: 1, 2, 3 and 4 represent gallstone, hypertriglyceridaemia, alcohol and other aetiologies, respectively.
MAP: mild acute pancreatitis; MSAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; BISAP: bedside index for severity in AP; RDW: red cell distribution width; NLR: neutrophil—lymphocyte ratio; LMR: lymphocyte—monocyte ratio; PLR: platelet lymphocyte ratio; TC: total calcium; ACC: albumin-corrected calcium; BUN: blood urea nitrogen.

Table 3 ORs of the prognostic factors for predicting SAP in patients with AP.

Factors	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
BISAP	2.729 (2.063 to 3.611)	0.000	3.074 (2.264 to 4.175)	0.000	2.115 (1.486 to 3.013)	0.000
NLR	1.074 (1.049 to 1.100)	0.000	1.076 (1.051 to 1.102)	0.019	1.054 (1.009 to 1.101)	0.018
PLR	1.004 (1.002 to 1.005)	0.000	1.004 (1.002 to 1.006)	0.000	1.000 (0.997 to 1.003)	0.851
LMR	0.614 (0.500 to 0.754)	0.000	0.613 (0.497 to 0.756)	0.000	1.060 (0.839 to 1.339)	0.627
TC	0.031 (0.010 to 0.099)	0.000	0.032 (0.010 to 0.102)	0.000	0.089 (0.024 to 0.328)	0.000
ACC	2.718 (1.331 to 5.551)	0.006	2.971 (1.328 to 6.646)	0.008	1.422 (0.577 to 3.508)	0.444
BUN	1.160 (1.074 to 1.252)	0.000	1.168 (1.076 to 1.269)	0.000	1.052 (0.945 to 1.174)	0.352
Creatinine	1.006 (1.002 to 1.011)	0.009	1.006 (1.001 to 1.011)	0.012	1.003 (0.995 to 1.010)	0.474
RDW	1.147 (0.938 to 1.499)	0.178	1.158 (0.946 to 1.420)	0.156	1.031 (0.820 to 1.300)	0.792

Model 1: unadjusted model.
Model 2: adjusted for age, sex and whether accompany a diabetes or liver failure.
Model 3: each marker was adjusted for age, sex, whether accompanied by diabetes or liver failure and eight other inflammatory markers.
BISAP: bedside index for severity in AP; RDW: red cell distribution width; NLR: neutrophil—lymphocyte ratio; LMR: lymphocyte—monocyte ratio; PLR: platelet lymphocyte ratio; TC: total calcium; ACC: albumin-corrected calcium; BUN: blood urea nitrogen.

($P = 0.003$) and TC ($P < 0.001$) were lower in the patients who did not experience organ failure (Table 2).

The relationship between inflammatory markers and the severity of AP

The multivariate logistic regression models revealed that higher NLR (adjusted OR = 1.053, 95% CI: 1.009 to 1.101, $P = 0.019$) and lower TC (adjusted OR = 0.088, 95% CI: 0.024 to 1.030, $P < 0.001$) also were independent factors for predicting SAP in patients with AP, had the same role as BISAP score (adjusted OR = 2.117, 95% CI: 1.487 to 3.016, $P < 0.001$) (Table 3).

Predictive value of the inflammatory markers compared to the BISAP score in patients with and those without POF

We described the ROC curve of all inflammatory markers for predicting POF in all patients (Fig. 1). For all AP patients, same as the BISAP score ($P < 0.001$), higher NLR, PLR, ACC, BUN, creatinine, RDW and lower LMR, TC predicted POF

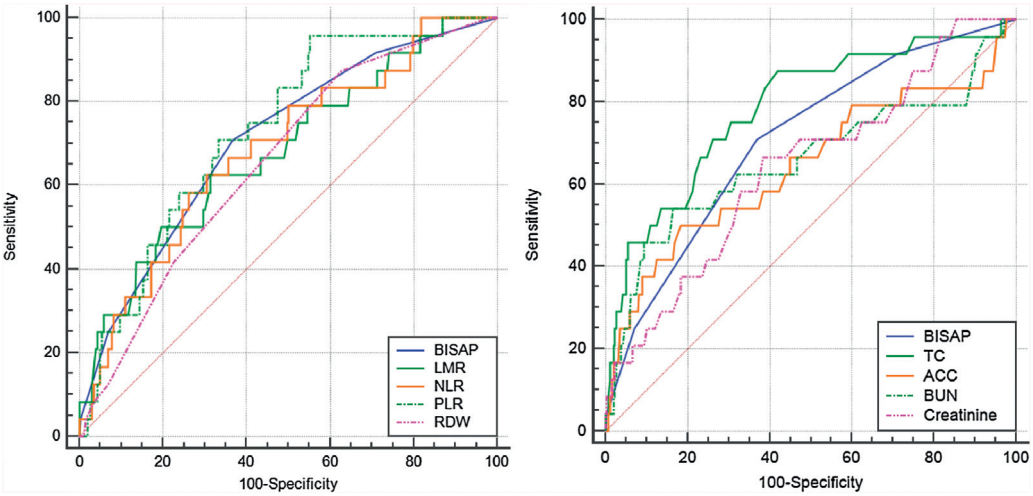

Figure 1 Receiver operating characteristic (ROC) curve analysis for predicting the occurrence of organ failure by all inflammation markers in the estimation cohorts.

Table 4 dentification of inflammatory markers in the patients with AP and organ failure.

Variable	AUC	*P*-value	Cut-off	Sensitivity (%)	Specificity (%)	+LR	−LR
BISAP	0.708 (0.651 to 0.761)	0.000	1	70.83	63.14	1.92	0.46
NLR	0.684 (0.626 to 0.739)	0.001	14.05	58.33	73.73	2.22	0.57
PLR	0.731 (0.675 to 0.782)	0.000	173.13	95.84	44.71	1.73	0.093
ACC	0.643 (0.584 to 0.699)	0.041	2.45	50.0	81.57	2.71	0.61
BUN	0.658 (0.599 to 0.713)	0.028	7.36	54.17	83.53	3.29	0.55
Creatinine	0.640 (0.581 to 0.697)	0.020	65.0	66.67	61.57	1.73	0.54
LMR	0.680 (0.622 to 0.735)	0.002	1.29	62.50	68.63	1.99	0.55
TC	0.784 (0.731 to 0.831)	0.000	2.18	87.5	57.65	2.07	0.22
RDW	0.656 (0.597 to 0.712)	0.004	12	87.5	37.25	1.39	0.34

BISAP: bedside index for severity in AP; RDW: red cell distribution width; NLR: neutrophil—lymphocyte ratio; LMR: lymphocyte—monocyte ratio; PLR: platelet lymphocyte ratio; TC: total calcium; ACC: albumin-corrected calcium; BUN: blood urea nitrogen.

Table 5 Comparison of ROC curves with BISAP.

Other marker	BISAP				
	Difference between areas	Standard error	95% confidence interval	z statistic	*P*-value
NLR	0.023	0.058	−0.091 to 0.138	0.402	0.687
PLR	0.023	0.062	−0.099 to 0.145	0.377	0.706
ACC	0.065	0.081	−0.094 to 0.223	0.799	0.424
BUN	0.050	0.081	−0.109 to 0.210	0.617	0.537
Creatinine	0.068	0.075	−0.079 to 0.214	0.902	0.367
LMR	0.028	0.064	−0.098 to 0.153	0.432	0.666
TC	0.076	0.063	−0.047 to 0.199	1.209	0.227
RDW	0.052	0.071	−0.088 to 0.191	0.724	0.469

P [a] Hanley and McNeil, 1983.
BISAP: bedside index for severity in AP; RDW: red cell distribution width; NLR: neutrophil—lymphocyte ratio; LMR: lymphocyte—monocyte ratio; PLR: platelet lymphocyte ratio; TC: total calcium; ACC: albumin-corrected calcium; BUN: blood urea nitrogen.

with statistical significance ($P = 0.001$, $P = 0.002$, $P < 0.001$, $P < 0.001$, $P = 0.041$, $P = 0.028$, $P = 0.020$, $P = 0.004$). Among the above indicators, TC and PLR had an AUC that were not inferior to BISAP score (TC 0.784, PLR 0.731, BISAP 0.708), they all predicted the POF well. When the value of the indicators were at the best cut-off value, PLR had the best sensitivity (95.8%), BUN had the best specificity (44.71%), respectively (Table 4). The AUCs of the NLR, LMR, PLR, TC,

ACC, BUN, creatinine and RDW were not significantly different from that of the BISAP score (Table 5).

Discussion

In the present study, we compared the prognostic value of general inflammation-based prognostic markers with the more mature scoring system BISAP in the same patients. We found that same as the BISAP, NLR, PLR, LMR, TC, ACC, BUN, creatinine and RDW have correlation with severity of AP. The BISAP score, NLR and TC can be used as independent predictors of the severity of pancreatitis. The ROC curve results indicated that most of the inflammation-based markers could predict whether the organ failure would occur or not, and of these, TC and PLR had the AUC that was not inferior to BISAP score, they all predicted the POF well. When the value of the indicators were at the best cut-off value, PLR had the best sensitivity, BUN had the best specificity, respectively.

AP is an inflammatory disease, with mortality arising mainly from organ failure or infected pancreatic necrosis [20]. In severe pancreatitis, various cytokines such as IL-1, IL-6, IL-8, TNF-a, platelet activating factor (PAF) and complement C5a in circulating blood can chemotaxis and activate neutrophils, monocytes, lymphocytes and platelets [21,22]. However, neutrophil apoptosis is delayed by extracellular signal-regulated kinase (ERK), c-Jun amino (2) terminal kinase (JHK), NK-kappa B, and signal transducers and activators of transcription (STAT) Ion [23], which increases the number of white blood cells and neutrophils in the peripheral blood, leading to aggravation of AP inflammation. Meantime, vascular endothelial damage and coagulation dysfunction associated with severe pancreatitis can also activate platelets and white blood cells [11]. But due to the overexpression of Fas/FasL, the apoptosis of peripheral blood lymphocytes is relatively increased in acute pancreatitis [24]. Therefore, the proportion of various cells in the peripheral blood changes, and with the severity of pancreatitis, this change is becoming more and more serious. In our study, as the illness worsened, the NLR and PLR gradually increased (all $P < 0.05$), the LMR decreased ($P < 0.001$). NLR could be used as independent factors to predict the severity of pancreatitis. And higher NLR, PLR, and lower LMR also predicted POF with statistical significance (AUC of NLR was 0.684, $P = 0.001$; AUC of PLR was 0.731, $P = 0.000$; AUC of LMR was 0.680, $P = 0.002$). This is similar to other studies [13,14,25]. However, Binnetoglu et al. [17] reported that the prognostic value of NLR is controversial in patients with AP. Because antibiotics could affect leukocyte counts by reducing the inflammatory process, they found different results after early antibiotic treatment, and the treatment started after the appearance of pancreatic necrosis [26]. Because antibiotics affect not only the ratio of neutrophils and lymphocytes but also most blood components, including mononuclear cells and platelets. In this study, we excluded the patients who accepted treatment before blood collection.

Red blood cell distribution width (RDW), reported as a part of the complete blood count test, is a quantitative measure of variability in the size of circulating erythrocytes [27]. RDW is mainly used as a diagnostic method to differentiate thalassemia from iron deficiency anemia [28]. As mentioned early, Senol et al.'s study also reported that the RDW on admission could be a predictor for mortality in patients with AP [29]. Yao studied a total of 106 patients with AP and 204 healthy individuals, found the RDW values were non-survivors of patients with AP > healthy individuals > survivors of patients with AP [30]. The result of this cohort suggested the RDW was not associated with the severity of pancreatitis, but when predicted the occurrence of POF, which implied a higher mortality. The result was similar to Azita et al.'s research [31]. They thought RDW was not a strong prognostic marker for AP, and recommend studying its combination with other prognostic markers. The underlying mechanism for the observed association between RDW and mortality in AP is not clear. One suggested explanation is that Inflammation increases RDW by promoting death and inhibiting maturation of RBCs through Additionally, inflammation changes the morphology of RBCs by altering their membrane glycoproteins and ion channels, allowing reticulocytes to enter the circulation [32].

A rise in the BUN level reflects the disease status of initial intravascular volume depletion and prerenal azotemia in AP [16]. A body of evidences suggested that it is an important predictor for the assessment of SAP. An international validation study noted that a BUN level of 7.12 mmol/L or a higher one was associated with increased incidence of mortality (OR: 4.6, 95% CI: 2.5—8.3) [33]. In our study, the cut-off value of BUN was 7.36 mmol/L, it has a relationship with the severity of pancreatitis ($P = 0.001$) and could predict the occurrence of POF (AUC = 0.658, $P = 0.028$). Creatinine was not related to the severity of pancreatitis, but only the occurrence of POF (AUC = 0.640, $P = 0.020$).

Various experiments and studies in 1990's showed that hypocalcemia was due to the raised glucagon levels in AP and hypocalcemia occurred due to decreased release of calcium from the skeleton as a result of calcitonin release stimulated by glucagon [34,35]. Another explanation given for hypocalcemia in AP was the low magnesium levels, which render the target organs resistant to the actions of parathyroid hormone [36]. In our study, with the aggravation of pancreatitis, TC and ACC gradually decreased. Decreased TC and ACC were related to the severity of AP and the occurrence of the POF. They were useful severity predictors in acute pancreatitis. It was consistent with Chhabra et al.'s [37] and Pokharel et al.'s study [38]. TC was with a 2.18 mmol/L cut-off value, sensitivity of 87.5% and specificity of 57.65% for predicting the occurrence of POF, ACC was with a 2.45 mmol/L cut-off value, sensitivity of 50.0% and specificity of 81.57%. TC has a larger AUC than ACC (0.784 vs. 0.643), and could be used as an independent predictors of the severity of pancreatitis, it had a prognostic value that was not weaker than BISAP. TC seems to be better as the value of ACC varied with various other parameters including the nutritional status and chronic liver disease, and it also takes a little time for albumin to get depleted in diseases [38].

BISAP is a system for judging the severity of pancreatitis. It is simple to identify patients with a high risk of death and those at a high risk of developing SAP in 24 h and has been proven to be an accurate risk stratification score standard [39]. When predicted the occurrence of POF, the AUC of BISAP in this study was 0.708, with a 1.0 cut-off value, this AUC is lower than that of Wu et al.'s study (AUC = 0.802),

which may be related to the different purpose of prediction. Wu et al.'s AUC of BISAP is mainly about predicting mortality of AP [6], but the AUC of BISAP in our study was mainly about the occurrence of persistent organ failure. Same as the BISAP, NLR, PLR, LMR, TC, ACC, BUN, creatinine and RDW had a correlation with severity of AP. According to the ROC curves, most of these markers have value for predicting the occurrence of POF, the AUC between BISAP and the studied inflammatory markers had no significant difference. Although there was no statistical significance, the TC and PLR had better AUC (0.784, 0.731). The result of TC was consistent with the study by Pokharel et al. (AUC = 0.787) [15]. The result of PLR was higher than Cho et al.'s study (AUC = 0.683), who reported PLR can predict the severity of AP only in gallstone AP. Among these predictors, the PLR had a better sensitivity (95.8%) and specificity (44.7%), this is also higher than Cho et al.'s study (sensitivity 70.4%, specificity52.3%) [14]. these inflammatory markers are more inexpensive, convenient and economic in clinical settings and have the same predictive function.

Conclusion

In conclusion, we find that compared with BISAP score, NLR and TC could also be used as independent factors to predict the severity of pancreatitis. The NLR, LMR, PLR, TC, ACC, BUN, creatinine and RDW have the same prognostic value as BISAP for POF. NLR and TC are the most powerful marker in this patient series, they have the same predictive power as BISAP, and are equally simple, rapid. When applying these markers, all possible influences from therapy should be considered.

Limitations

This study has several limitations. First, the number of patients enrolled in this study was small. Second, we did not compare inflammatory markers with other biochemical markers and the Grading standards, such as Ranson and modified Glasgow score and APACHE-II, so the results have some limitations. Third, we did not describe the changes in these inflammatory markers during treatment, which could help better predict the prognosis of AP. Despite these limitations, this study also has some strengths. Most laboratory values were obtained within 24 h of initial presentation before accepting treatment to minimize the changes in WBC and platelet counts caused by hydration and medication. The effect of antibiotics was excluded. This is the first study investigating the predictive value of inflammatory markers with the mature scoring system BISAP.

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Disclosure of interest

The authors declare that they have no competing interest.

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