BMJ Open

Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study

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ABSTRACT

Objectives: Inflammation-based prognostic markers (neutrophil–lymphocyte ratio (NLR), prognostic nutritional index (PNI), red cell distribution width (RDW) and lymphocyte–monocyte ratio (LMR)) are associated with overall survival in some diseases. This study assessed their prognostic value in mortality and severity in acute pancreatitis (AP).

Design: A retrospective cohort study.

Setting: Patients with AP were recruited from the emergency department at our hospital.

Participants: A total of 359 patients with AP (31 non-survivors) were enrolled.

Primary and secondary outcome measures: Mortality and severity of AP were the primary and secondary outcome measures, respectively. Biochemistry and haematology results of the first test after admission were collected. Independent relationships between severe AP (SAP) and markers were assessed using multivariate logistic regression models. Mortality prediction ability was evaluated using receiver operating characteristic (ROC) curves. Overall survival was evaluated using the Kaplan-Meier method, with differences compared using the log-rank test. Independent relationships between mortality and each predictor were estimated using the Cox proportional hazard models.

Results: Compared with survivors of AP, non-survivors had higher RDW (p<0.001), higher NLR (p<0.001), lower LMR (p<0.001) and lower PNI (p<0.001) at baseline. C reactive protein (CRP; OR=8.251, p<0.001), RDW (OR=2.533, p=0.003) and PNI (OR=7.753, p<0.001) were independently associated with the occurrence of SAP. For predicting mortality, NLR had the largest area under the ROC curve (0.804, p<0.001), with a 16.64 cut-off value, 82.4% sensitivity and 75.6% specificity. RDW was a reliable marker for excluding death owing to its lowest negative likelihood ratio (0.11). NLR (HR=4.726, p=0.004), CRP (HR=3.503, p=0.003), RDW (HR=3.139, p=0.013) and PNI (HR=2.641, p=0.011) were independently associated with mortality of AP.

Conclusions: NLR was the most powerful marker of overall survival in this patient series.

INTRODUCTION

Acute pancreatitis (AP) is rapid-onset inflammation of the pancreas that varies in severity from a self-limiting mild illness to rapidly

Strengths and limitations of this study

- Compared with survivors of acute pancreatitis (AP), non-survivors had higher red cell distribution width (RDW) and neutrophil–lymphocyte ratio (NLR), and lower lymphocyte–monocyte ratio (LMR) and prognostic nutritional index (PNI) at baseline.
- NLR exhibited a higher area under the receiver operating characteristic curve for the prediction of mortality compared with other markers.
- RDW was suitable as a reliable marker to exclude death.
- NLR, PNI, C reactive protein and RDW were independently associated with overall survival of AP.
- This was a retrospective cohort analysis.

progressive multiple organ failure. Statistics suggest that 10–20% of patients with AP develop severe AP (SAP),[1] which usually has an unfavourable disease progression and is associated with a poor prognosis.[2] [3] Prediction of disease severity can guide the management of patients with AP and improve the outcome. Organ failure and infected pancreatic necrosis are common causes of mortality in such patients,[4] and a new international multidisciplinary classification of SAP incorporates both events as determinants of severity.[5] The predictive values of various markers, such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Bedside Index of Severity in Acute Pancreatitis scores, C reactive protein (CRP) and procalcitonin, have been previously assessed.[6–8] A systematic review concluded that it was justifiable to use blood urea nitrogen after 48 hours of hospital admission for predicting persistent organ failure.[9] In clinical studies, most studies have focused on disease severity, and only a few have directly investigated the relationship between predictors and mortality of AP. Furthermore, no reliable predictor of

persistent organ failure within 48 hours of admission has been identified.[9]

There is increasing evidence that the presence of a systemic inflammatory response is associated with poor survival in patients with various aetiologies, including malignancy.[10–17] Many direct or combined markers of systemic inflammation are based on routine, inexpensive and readily available laboratory tests. Red cell distribution width (RDW),[10] neutrophil–lymphocyte ratio (NLR), prognostic nutritional index (PNI)[11] and lymphocyte–monocyte ratio (LMR)[12] have been used to predict the prognosis of disease. RDW was found to be an independent marker of short-term and long-term prognosis in intensive care units.[10] NLR at admission served as an independent predictor of 3-month mortality rates in patients with acute-on-chronic liver failure.[13] Increased pretreatment LMR was associated with a significantly more favourable prognosis in patients with solid tumours.[12] Despite this evidence, very few studies have focused on the direct relationship between inflammation-based prognostic markers and mortality of AP. A cross-sectional study found a significant association between RDW and mortality in patients with AP.[18] Another study investigated the prognostic value of NLR in AP and determined an optimal ratio for prediction of severity.[19]

To the best of our knowledge, the current study is the first to simultaneously compare the prognostic value of these inflammation-based prognostic markers (NLR, PNI, CRP, RDW and LMR) of mortality in patients with AP.

MATERIALS AND METHODS
Participants
This retrospective cohort analysis consecutively enrolled a series of patients with AP who were admitted to the emergency department at our hospital between 1 July 2013 and 18 August 2015. A diagnosis of AP required two of three features: (1) prolonged abdominal pain characteristic of AP, (2) threefold elevation of serum amylase and/or lipase levels above the normal range, and (3) characteristic findings of AP on abdominal ultrasonography and/or CT scan.[1] Mild AP (MAP) was defined as an absence of organ failure and an absence of local or systemic complications.[1] Moderately SAP (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).[1] Patients with recurrent pancreatitis were enrolled only at first admission. Patients with traumatic pancreatitis, autoimmune pancreatitis, diabetes mellitus, tumour or liver failure were excluded.

The prognostic information we focused on included overall survival and the severity of the disease. All enrolled patients were followed for 100 days or until death. All clinical data were retrieved from medical records. For patients with AP, 100 days of prognostic information (survival or non-survival) was obtained by checking medical records or by contacting the patients' family members.

Ethics statement
Each participant provided written informed consent after being provided with an explanation of the study by phone, letter or email. The study was conducted in accordance with the ethical principles contained within the Declaration of Helsinki.

Demographic information and laboratory analysis
Demographic information, including age, sex, aetiology and complication, was collected from medical records. Pretreatment laboratory data, including complete blood counts, serum CRP, albumin and amylase, were obtained during the emergency visit. An XE-2100 haematology autoanalyser (Sysmex Corp, Kobe, Japan), a Hitachi 7600 chemistry analyser (Hitachi High-Technologies, Tokyo, Japan) and Roche reagents (Roche Diagnostics, Indianapolis, Indiana, USA) were used in the laboratory.

We assessed the prognostic value of general inflammation-based prognostic markers (NLR, CRP, RDW, PNI and LMR) for predicting the mortality of AP. Additionally, their ability to predict the severity of AP (SAP or not SAP) was assessed. NLR and LMR were ratios of two types of blood cell. PNI=albumin (g/L) +5×total lymphocyte count (10^9/L).

Statistical analysis
Variables are expressed as mean±SD or median (range) and categorical data as percentages, as appropriate. Differences between the two groups were assessed using an independent sample t-test, Mann-Whitney U test or χ^2 test, as appropriate. Multiple comparisons were performed by one-way analysis of variance or Kruskal-Wallis H tests, as appropriate. The Bonferroni method was used to adjust for multiple comparisons. Multivariate logistic regression analyses were used to assess whether the inflammation markers were independent factors for predicting SAP in patients with AP by unadjusted and adjusted models successively. Patients with AP were randomly divided into estimation and validation cohorts by random number generators. The accuracy of each marker to predict mortality was assessed using receiver operating characteristic (ROC) curves. The sensitivity, specificity, positive likelihood ratio (+LR) and negative likelihood ratio (−LR) were calculated. +LR represents the ratio of the true-positive rate to the false-positive rate. −LR represents the ratio of the false-negative rate to the true-negative rate. These two parameters, which are not influenced by prevalence rate, are stable and objective for assessing diagnostic value. Combination models were developed using binary logistic regression analyses. Overall survival curves were calculated using the Kaplan-Meier method, and differences in survival rates were compared using the log-rank test. Univariate

and multivariate Cox proportional hazard models were used to estimate the significance and independence of the relationship of each marker and mortality. The variables with a p value <0.1 in univariate analysis were included in a multivariate Cox proportional hazard regression model. A p value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS V.19.0 (SPSS, Chicago, Illinois, USA).

RESULTS
Patient characteristics
A total of 359 patients with AP (197 MAP, 76 MSAP and 86 SAP) were enrolled in the study. The predefined probability of type I error was 0.05 (α=0.05), and the sample size was large enough to guarantee 0.90 of test power (β=0.1). Forty-five patients were excluded from the analysis, including those with traumatic pancreatitis (n=1), autoimmune pancreatitis (n=5), diabetes mellitus (n=7), tumour (n=7), liver failure (n=2) or incomplete medical records or who were lost to follow-up (n=23). Tables 1 and 2 show the baseline characteristics of the patients. There were no significant differences in age (p=0.352), aetiology (p=0.875) or sex (p=0.919) among the three groups (MAP, MSAP and SAP). As the illness worsened, CRP, RDW and NLR gradually increased, but PNI decreased (all p<0.05; table 1). LMR decreased significantly (p<0.001) in patients with MSAP compared with patients with MAP, but there was no significant difference between patients with MSAP and patients with SAP (p=0.883).

Compared with survivors of AP, non-survivors were older (p=0.001) and had higher CRP (p<0.001), amylase (p=0.010), RDW (p<0.001) and NLR (p<0.001). Conversely, lymphocyte count (p<0.001), platelets (p=0.001), albumin (p<0.001), LMR (p<0.001) and PNI (p<0.001) were lower in non-survivors than in survivors (table 2).

The relationship between markers and severity of AP
The multivariate logistic regression models revealed that high CRP (>110 vs ≤110 mg/L, adjusted OR=8.251, 95% CI 3.897 to 17.468, p<0.001), RDW (>13.0% vs ≤13.0%, adjusted OR=2.533, 95% CI 1.365 to 4.702, p=0.003) and low PNI (<41.1 vs ≥41.1, adjusted OR=7.753, 95% CI 3.400 to 17.680, p<0.001) were independent factors for predicting SAP in patients with AP (table 3).

The markers' power for predicting 100 days mortality
The enrolled 359 patients with AP were randomly grouped into two cohorts: the estimation cohort (n=181) and the validation cohort (n=178). No significant difference was observed between the estimation and the validation cohorts in all characteristics (see online supplementary table S1). ROC curves of the estimation cohort were constructed to evaluate the ability of each marker to predict 100 days mortality in AP. Table 4 shows the area under the ROC curves (AUC) and optimal cut-off values. The ability

Table 1 Demographics and laboratory findings in patients with acute pancreatitis

Variables	(1) MAP (n=197)	(2) MSAP (n=76)	(3) SAP (n=86)	p Value		
				All groups	1 vs 2	2 vs 3
Age (years)	51.43±16.00	48.47±13.28	50.69±14.61	0.352	0.446	1.000
Male (%)	108 (54.8%)	41 (53.9%)	49 (57.0%)	0.919	0.896	0.699
Aetiology (1/2/3/4)%	52%/12%/11%/25%	51%/16%/13%/20%	47%/15%/14%/24%	0.875	0.664	0.892
WCC (×10^9/L)	11.5 (3.1–32.0)	14.1 (4.5–36.8)	16.05 (5.9–38.4)	<0.001	<0.001	0.278
Lymphocyte (×10^9/L)	1.1 (0.2–9.4)	1.0 (0.2–2.6)	0.80 (0.2–2.9)	<0.001	0.004	0.089
Platelet (×10^9/L)	202 (21–502)	193 (58–548)	163 (27–540)	0.004	0.376	0.046
Albumin (g/L)	38.29±5.07	34.38±6.39	29.99±5.35	<0.001	<0.001	<0.001
CRP (mg/L)	53.9 (0.7–386)	133.6 (3.2–436.5)	196.1 (27.1–426.7)	<0.001	<0.001	<0.001
Amylase (U/L)	398 (13–5191)	222 (27–3845)	581 (16–2377)	0.141	0.083	0.056
RDW (%)	12.8 (11.4–19.2)	13.0 (11.3–16.3)	13.7 (11.7–23.6)	<0.001	0.013	0.014
NLR	8.46 (1.33–55)	14.60 (1.73–60)	19.65 (3.57–53.67)	<0.001	<0.001	0.020
LMR	1.88 (0.28–13.33)	1.03 (0.29–5.33)	1.14 (0.22–6.32)	<0.001	<0.001	0.883
PNI	44.53±6.63	39.36±6.71	34.55±6.02	<0.001	<0.001	<0.001
Mortality (%)	0 (0%)	0 (0%)	31 (36.0%)	<0.001	–	<0.001

Continuous variables are presented as mean±SD or median (range).
Aetiology (1/2/3/4)%, 1, 2, 3 and 4 represent gallstone, alcohol, hypertriglyceridaemia and other aetiologies, respectively.
1 vs 2, MAP group versus MSAP group; 2 vs 3, MSAP group versus SAP group.
CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width; SAP, severe acute pancreatitis; WCC, white cell count.

Table 2 Demographics and laboratory findings in survivors and non-survivors of acute pancreatitis

Variables	Survivors (n=328)	Non-survivors (n=31)	p Value
Age (years)	49.84±14.88	58.90±15.60	0.001
Male (%)	179 (54.6%)	19 (61.3%)	0.472
Aetiology (1/2/3/4)%	50%/13%/12%/25%	58%/19%/10%/13%	0.346
WCC (×10^9/L)	12.85 (3.1–38.4)	18.5 (6.5–29.3)	0.001
Lymphocytes (×10^9/L)	1.08 (0.17–9.40)	0.60 (0.30–1.60)	<0.001
Platelet (×10^9/L)	197 (21–548)	159 (27–376)	0.001
Albumin (g/L)	35.95±6.30	30.44±5.54	<0.001
CRP (mg/L)	98.6 (0.7–436.5)	239.2 (27.1–398.2)	<0.001
Amylase (U/L)	343.5 (13–5191)	909 (16–2377)	0.010
RDW (%)	13 (11.3–19.2)	13.8 (12.6–23.6)	<0.001
NLR	10.47 (1.33–60.0)	25.0 (8.67–53.67)	<0.001
PNI	41.71±7.50	34.00±6.35	<0.001
LMR	1.51 (0.22–13.33)	1.13 (0.24–2.26)	<0.001

Continuous variables are presented as mean±SD or median (range).
Aetiology (1/2/3/4)%, 1, 2, 3 and 4 represent gallstone, alcohol, hypertriglyceridaemia and other aetiologies, respectively.
CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width; WCC, white cell count.

Table 3 ORs of 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
NLR (>11.36 vs ≤11.36)	3.707 (2.173 to 6.326)	<0.001	3.578 (2.082 to 6.149)	<0.001	1.463 (0.711 to 3.010)	0.301
CRP(>110 vs ≤110 mg/L)	9.867 (5.116 to 19.030)	<0.001	12.609 (6.304 to 25.218)	<0.001	8.251 (3.897 to 17.468)	<0.001
RDW (>13.0% vs ≤13.0%)	3.368 (2.003 to 5.663)	<0.001	3.529 (2.076 to 5.998)	<0.001	2.533 (1.365 to 4.702)	0.003
PNI (<41.1 vs ≥41.1)	9.951 (5.055 to 19.589)	<0.001	11.356 (5.665 to 22.766)	<0.001	7.753 (3.400 to 17.680)	<0.001
LMR (<1.43 vs ≥1.43)	2.564 (1.539 to 4.271)	<0.001	2.552 (1.524 to 4.274)	<0.001	0.722 (0.355 to 1.471)	0.370

Model 1: unadjusted model.
Model 2: adjusted for age, gender and amylase.
Model 3: NLR was adjusted for age, gender, amylase, CRP, RDW, PNI and LMR; CRP was adjusted for age, gender, amylase, NLR, RDW, PNI and LMR; RDW was adjusted for age, gender, amylase, CRP, NLR, PNI and LMR; PNI was adjusted for age, gender, amylase, NLR, CRP, RDW and LMR; LMR was adjusted for age, gender, amylase, NLR, CRP, RDW and PNI.
AP, acute pancreatitis; CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width; SAP, severe acute pancreatitis.

of NLR to predict mortality (AUC=0.804, p<0.001) was good; those of PNI (AUC=0.769, p<0.001), CRP (AUC=0.774, p<0.001), RDW (AUC=0.769, p<0.001) and LMR (AUC=0.744, p<0.001) were fair. The NLR had the largest AUC, and RDW and PNI had the highest sensitivity and specificity, respectively. Therefore, these three markers were selected for combination. The AUC for NLR+PNI, NLR+RDW and PNI+RDW were 0.825 (95% CI 0.761 to 0.877), 0.854 (95% CI 0.794 to 0.902) and 0.806 (95% CI 0.741 to 0.861), respectively (figure 1). There were no significant differences in AUC for combined index and NLR (p=0.699, p=0.167 and p=0.975, respectively).

For NLR, the optimal cut-off value for mortality prediction was 16.64, with a sensitivity of 82.4% and specificity of 75.6%. RDW had the highest sensitivity (94.1%) and lowest −LR (0.11), so it was a reliable predictive index for excluding mortality in patients with AP. PNI had the highest specificity (88.4%) and +LR (5.08), so it was most suitable for use as a confirmed index among the indexes assessed.

In the validation cohort, AUCs for NLR, CRP, RDW, PNI and LMR were 0.851 (95% CI 0.790 to 0.900), 0.753 (95% CI 0.683 to 0.815), 0.708 (95% CI 0.635 to 0.773), 0.791 (95% CI 0.724 to 0.848) and 0.677 (95% CI 0.603 to 0.745), respectively. There were no significant differences in AUC for NLR, CRP, RDW, PNI and LMR between the estimation and validation cohorts (p=0.477, p=0.809, p=0.437, p=0.782 and p=0.455, respectively).

Survival analysis

Patients with AP were stratified into groups by cut-off values. Kaplan-Meier survival curves demonstrate the relationships between inflammation-based prognostic markers and overall survival of patients with AP (figure 2A−E). Elevated NLR (p<0.001), CRP (p<0.001) and RDW (p<0.001) were associated with increased probability of death. Conversely, decreased PNI (p<0.001) and LMR (p=0.001) were associated with decreased overall survival.

According to the cut-off values for the factors, low NLR (≤16.64), low CRP (≤162.2 mg/L), low RDW

Table 4 Discriminatory ability of inflammation-based markers for predicting mortality in patients with AP

Index	AUC (95% CI)	p Value*	Cut-off†	Sensitivity (%)	Specificity (%)	+LR	−LR
Training cohort							
NLR	0.804 (0.738 to 0.859)	<0.001	16.64	82.4	75.6	3.38	0.23
CRP	0.774 (0.706 to 0.833)	<0.001	162.2 mg/L	76.5	73.8	2.92	0.32
RDW	0.769 (0.700 to 0.828)	<0.001	13.0%	94.1	54.3	2.06	0.11
PNI	0.769 (0.701 to 0.828)	<0.001	33.1	58.8	88.4	5.08	0.47
LMR	0.744 (0.674 to 0.806)	<0.001	1.40	82.4	57.3	1.93	0.31
Validation cohort							
NLR	0.851 (0.790 to 0.900)	<0.001	16.64	85.7	73.8	3.27	0.19
CRP	0.753 (0.683 to 0.815)	<0.001	162.2 mg/L	71.4	65.2	2.06	0.44
RDW	0.708 (0.635 to 0.773)	0.001	13.0%	85.7	50.0	1.71	0.29
PNI	0.791 (0.724 to 0.848)	<0.001	33.1	42.9	88.4	3.70	0.65
LMR	0.677 (0.603 to 0.745)	0.015	1.40	78.6	49.4	1.55	0.43
Overall							
NLR	0.823 (0.780 to 0.861)	<0.001	16.64	83.9	74.4	3.27	0.22
CRP	0.762 (0.714 to 0.805)	<0.001	162.2 mg/L	74.2	69.8	2.46	0.37
RDW	0.742 (0.693 to 0.786)	<0.001	13.0%	90.3	49.7	1.80	0.19
PNI	0.781 (0.734 to 0.822)	<0.001	33.1	51.6	88.4	4.46	0.55
LMR	0.710 (0.660 to 0.757)	<0.001	1.40	77.4	54.0	1.68	0.42

*The p value is comparing the AUC with 0.5.
†The cut-off values were derived from a training cohort.
−LR, negative likelihood ratio; +LR, positive likelihood ratio; AP, acute pancreatitis; AUC, area under the receiver operating characteristic curve; CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width.
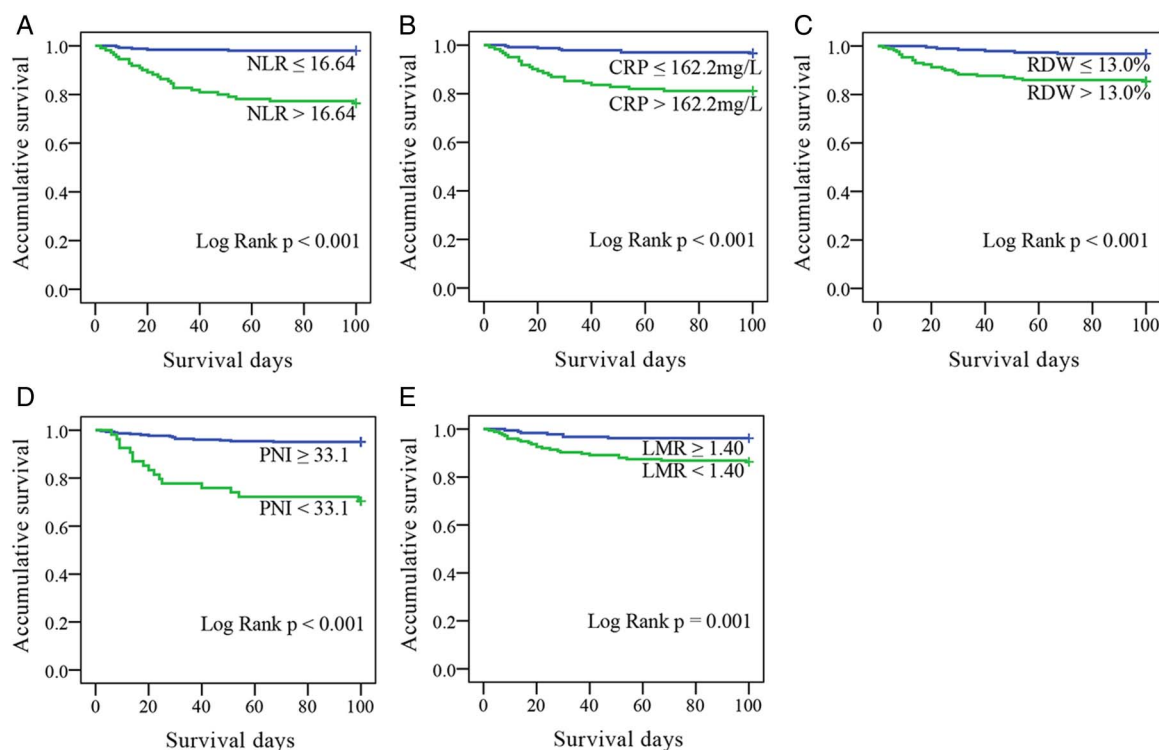
Figure 1 ROC curves analysis for predicting mortality by NLR and combined markers in the estimation cohort. ROC, receiver operating characteristic; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width.

(≤13.0%), high PNI (>33.1) and high LMR (>1.40) were selected as references. Univariate analysis and Cox regression revealed that age (p<0.001), amylase (p=0.001), NLR (p<0.001), PNI (p<0.001), CRP (p<0.001), RDW (p<0.001) and LMR (p=0.002) were associated with AP mortality (table 5). These factors were evaluated using multivariate Cox regression. Age (HR=4.039, 95% CI 1.873 to 8.713, p<0.001), NLR
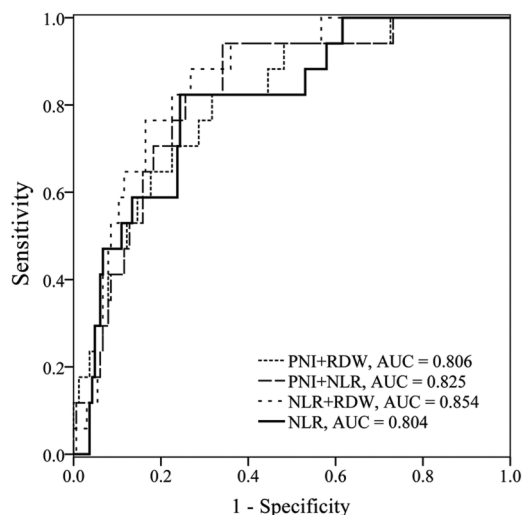
Figure 2 Relationship between inflammation-based prognostic markers and overall survival in patients with acute pancreatitis. A, B, C, D and E show the relationship between NLR, CRP, RDW, PNI and LMR, and overall survival in patients with acute pancreatitis, respectively. CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width.

(HR=4.726, 95% CI 1.627 to 13.726, p=0.004), CRP (HR=3.503, 95% CI 1.534 to 7.999, p=0.003), RDW (HR=3.139, 95% CI 1.277 to 7.714, p=0.013) and PNI (HR=2.641, 95% CI 1.248 to 5.590, p=0.011) were independently associated with mortality of AP (table 5).

DISCUSSION

AP is an inflammatory disease, with mortality arising mainly from organ failure or infected pancreatic necrosis.[4] Our study estimated the prognostic value of various inflammation-based prognostic markers for predicting mortality of AP. According to classifications of AUC,[20 21] the ability of the NLR to predict mortality was good, while those of PNI, CRP, RDW and LMR were fair. Cox regression analysis revealed that age, NLR, PNI, CRP

and RDW were independently associated with mortality of AP. Additionally, PNI, CRP and RDW were independently associated with the occurrence of SAP in patients with AP.

NLR, CRP, RDW and PNI are inexpensive, convenient and readily available in clinical settings. From examination of AUC, NLR had the best performance. With an NLR>16.64 at the time of admission, the risk of dying increased 3.726-fold compared with NLR≤16.64. RDW was the most reliable marker for excluding death in patients with AP, owing to its lowest −LR (0.11). PNI had the highest specificity (88.4%) and +LR (5.08), so it was most suitable to be a confirmed index among the indexes assessed. However, fluctuations in the NLR and CRP can be influenced by the use of antibiotics; therefore, NLR and CRP are not suitable for patients undergoing intensive use of antibiotics. Similarly, blood transfusion and parenteral nutrition may affect RDW and PNI, respectively, so the predictive value of RDW and PNI in these patients was discounted.

In AP, inflammation propagates and promotes tissue destruction via activation of a cascade of inflammatory cytokines, proteolytic enzymes and oxygen-free radicals.[19 22] Neutrophils, lymphocytes and monocytes are the three main types of white cell counts (WCC). Neutrophils play a key role in the development of local tissue destruction and systemic complications of SAP.[23] Depletion of neutrophils has been associated with an improved prognosis of AP.[23] The percentage of immature neutrophilic granulocytes might be used clinically as a simple early predictor of an adverse outcome in SAP.[24] Additionally, recent studies revealed that the extent of lymphopaenia was associated with disease severity.[25–27] Lymphopaenia has been reported to have independent prognostic value for some diseases,[19 26–29] including AP. Takeyama et al[28] found that impairment of cellular immunity caused by peripheral lymphocyte apoptosis was linked to the subsequent development of infectious complications in AP. Monocytes produce various cytokines and inflammatory mediators that further amplify inflammatory cell recruitment into the pancreas as well as distant organs such as the lungs.[30]

Table 5 Prognostic factors of overall survival in patients with acute pancreatitis by univariate and multivariate analyses

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (>63 vs ≤63 years)	5.384 (2.653 to 10.925)	<0.001	4.039 (1.873 to 8.713)	<0.001
Gender (female vs male)	0.767 (0.372 to 1.579)	0.471		
Amylase (>618 vs ≤618 U/L)	3.544 (1.699 to 7.526)	0.001	2.173 (0.965 to 4.891)	0.061
NLR (>16.64 vs ≤16.64)	13.130 (5.041 to 34.205)	<0.001	4.726 (1.627 to 13.726)	0.004
CRP (>162.2 vs ≤162.2 mg/L)	6.127 (2.740 to 13.701)	<0.001	3.503 (1.534 to 7.999)	0.003
RDW (>13.0% vs ≤13.0%)	4.929 (2.022 to 12.017)	<0.001	3.139 (1.277 to 7.714)	0.013
PNI (≤33.1 vs >33.1)	6.912 (3.414 to 13.991)	<0.001	2.641 (1.248 to 5.590)	0.011
LMR (≤1.40 vs >1.40)	3.797 (1.636 to 8.813)	0.002	1.036 (0.403 to 2.659)	0.942

CRP, C reactive protein; LMR, lymphocyte–monocyte ratio; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; RDW, red cell distribution width.

Similar to neutrophils, a protective effect was also found by depleting macrophages in a mouse model of AP.[31] Theoretically, NLR and LMR, which combine two opposing parameters, should be more accurate than either parameter alone. We found that the NLR had the greatest prognostic value of all the factors we evaluated. It is, however, important to apply the NLR with caution in clinical settings. Broad-spectrum antibiotics with good tissue penetration, which are essential medicines in the treatment of SAP, can affect WCC by reducing inflammation. Thus, the prognostic value of NLR in AP is uncertain if the effect of antibiotic treatment is not taken into account.[32] For this reason, the neutrophil and lymphocyte counts used in this study were from the first complete blood cell count conducted during the emergency visit. We confirmed that the enrolled patients were untreated at that time; consequently, our results are most likely applicable to untreated patients. Unlike for the NLR, the predictive ability of the LMR was only fair, and was not independently associated with overall survival in AP.

Serum albumin is a negative acute phase response reactant, and reflects the body's nutritional status. Albumin <25 g/L was an independent prognostic factor related to a poor prognosis of AP.[33] Variation of albumin within 24 hours has been identified as a risk factor for a poor prognosis of critically ill patients in the early stages of SAP.[34] The PNI, which includes serum albumin and lymphocyte count, is an independent predictor of poor overall survival in patients with hepatocellular carcinoma.[35] To the best of our knowledge, few studies have reported on the application of PNI for predicting mortality of AP, but we found that it was an independent prognostic factor, and was suitable as a confirmed marker.

Numerous studies have reported RDW as a strong independent prognostic factor in various diseases and conditions, such as cardiovascular diseases, rheumatoid arthritis, cancer and critical illnesses.[18 36–38] Our results are consistent with the study by Yao and Lv,[18] who reported a significant association between RDW and mortality of patients with AP. Additionally, we found that RDW was most suitable as a reliable excluding marker among the markers we assessed. The mechanisms underlying the association between RDW and mortality in AP remain unclear. The obvious metabolic abnormalities in non-survivors of AP, including inflammation, oxidative stress, poor nutritional status and persistent organ failure, lead to deregulation of red blood cell homoeostasis involving both impaired erythropoiesis and abnormal red blood cell survival.[38] RDW reflects these impairments in homoeostasis, but only further research can confirm this speculation.

The prognostic markers evaluated in this study are direct or combined markers of systemic inflammation that are based on routine, inexpensive and readily available laboratory tests. To the best of our knowledge, this is the first study to compare the prognostic value of these markers for predicting mortality in patients with AP simultaneously. Additionally, suitable excluding and identifying markers were found.

Some potential limitations of the study should be noted. Although we have taken special care to avoid sources of bias and confounding, some potential bias may still exist in this retrospective, single-centre study. Information available at the beginning of the study may have affected the selection of the study participants, although the medical records and laboratory data were collected separately by two people. The reasons for incomplete medical records or why patients were lost to follow-up (n=23) are not known. These patients were excluded from the analyses. As a result, a larger prospective study is needed to validate the results. Second, only the first set of admission blood results were investigated. Since factors change with time, they should be surveyed in the future because of the rapid onset of inflammation. Third, the typical prediction models, such as the APACHE II score, should be included in future research. Fourth, for better validity, +LR should be near 10, and −LR should be 0.2. Unfortunately, no marker examined had perfect +LR and −LR simultaneously. Therefore, the markers should be selected with caution based on particular needs. The marker with the higher +LR was more suitable to confirm death, while the marker with the lower −LR was more suitable to exclude death. Appropriate judgement based on the available information will be more reliable; however, these markers are still valuable based on their acceptable AUC. Finally, we only described the association of each of the predictors with mortality of AP; the underlying mechanisms need to be investigated.

In conclusion, we found that age, NLR, PNI, CRP and RDW were independently associated with overall survival of AP. NLR had the best overall performance, RDW was suitable as a reliable marker to exclude death, and PNI was a good predictive marker for death. When applying these markers, any possible influence from therapy should be considered.

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