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Association between red cell distribution width and acute pancreatitis: a cross-sectional study

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ABSTRACT

Objective: We investigated whether red cell distribution width (RDW) was associated with mortality in patients with acute pancreatitis (AP).

Design: A cross-sectional study.

Setting: Patients with AP were recruited in the emergency department and healthy individuals were recruited in healthcare centre in the First Affiliated Hospital of Zhejiang University.

Participants: A total of 106 patients with AP and 204 healthy individuals were enrolled.

Primary and secondary outcome measures: Haematology and biochemistry results of the first test after admission were collected. The significance of the differences in RDW values among healthy individuals, non-survivors of patients with AP, and survivors of patients with AP was determined using one-way analysis of variance. Patients with AP were divided into three groups according to RDW tertiles. All patients with AP were followed up for at least 3 months. Receiver-operating characteristic (ROC) curve analysis and Kaplan-Meier analysis were used to evaluate RDW values to predict mortality of patients with AP.

Results: The RDW values were non-survivors of patients with AP>healthy individuals>survivors of patients with AP. Patients with AP with the highest RDW tertiles had the lowest levels of Ca, total protein, albumin, haemoglobin, white and red blood cell count, but the highest mortality. The area under the ROC curve of RDW was 0.846 (95% CI 0.727 to 0.964, p<0.001). With a cut-off value of 14.2 for RDW, sensitivity and specificity of RDW to predict mortality were 75.0% and 89.8%, and Kaplan-Meier analysis showed an increase in probability of death with high RDW values.

Conclusions: There is significant association between RDW and mortality of patients with AP.

Strengths and limitations of this study

- Red cell distribution width (RDW) was significantly higher in severe acute pancreatitis than in mild acute pancreatitis and healthy individuals.
- RDW was significantly higher in non-survivors of AP than in healthy individuals and survivors of patients with acute pancreatitis (AP).
- RDW was significantly associated with mortality of patients with AP.
- Sensitivity and specificity of RDW to predict mortality were 75.0% and 89.8%.
- This was a cross-sectional and small sample study.

to express the results as percentages, and reflects the variability of the size of the circulating erythrocytes.[1] RDW is a traditional marker of excluding iron deficiency anaemia in case serum ferritin does not accurately indicate the total iron store, and plays a role in the differential diagnosis of anaemia.[2] Recent studies have reported that RDW as a strong and independent prognostic marker has been used in many pathophysiological conditions, such as cardiovascular diseases, pulmonary diseases, rheumatoid arthritis and progressive inflammatory status, and even cancer.[3–11]

Acute pancreatitis (AP), classified into mild acute pancreatitis (MAP) and severe acute pancreatitis (SAP), is a common surgical acute abdomen.[12] AP is often complicated with systemic inflammatory response syndrome and multiple organ failure, and the mortality rate in patients with AP is about 5–10%, in SAP about 10–30% in China.[12 13] Early predictive scores of SAP included Ranson and APACHE II scores, the testing parameters in the two scores are expensive, operation trival, and not conducive to clinical implementation.[14 15] The study of Wang *et al*[16] indicated some inexpensive and operation easy predictive factors had been used to predict the mortality of AP. RDW value has scarcely been investigated as

INTRODUCTION

Red cell distribution width (RDW) is a widely used laboratory parameter for the quantification of the extent of erythrocyte anisocytosis, which is calculated by dividing SD of red blood cells (RBCs) volume by mean corpuscular volume (MCV) and multiplying by 100

a potential biomarker of AP. Therefore, we aimed to investigate whether RDW was associated with the mortality of patients with AP.

MATERIALS AND METHODS
Patients
The study included 106 patients with AP admitted to the emergency department of the First Affiliated Hospital of Zhejiang University between 30 May 2011 and 30 May 2013, and 212 healthy individuals without chronic disease and abnormal physical examination matched for age, sex and race. Eight healthy individuals were excluded due to the absence of serum biochemistry and/or blood cell count. Patients with AP were included in the study according to the guidelines of diagnosis and treatment of AP established by the Branch of Gastroenterology, Chinese Medical Association in 2003.[12] The diagnosis of AP was as follows: (1) prolonged abdominal pain characteristic of AP; (2) elevated serum amylase (Amy) and/or lipase levels by at least threefold that of normal range and (3) characteristic findings of AP on abdominal ultrasonography and/or CT scan. MAP is characterised by the absence of organ failure and the absence of local or systemic complications.[12] SAP is characterised by persistent single or multiple organ failure, and usually accompanied by one or more local complications.[12]

Assays
Demographic data, aetiology of pancreatitis, hospitalisation time, laboratory serum biochemistry and complete blood cell count measures were recorded on admission. We collected samples from the 106 patients with onset of AP within 24 h for haematology and biochemistry detection on admission. White cell count (WCC), RBC count, platelet (PLT) count, RDW, haemoglobin (Hgb) level, MCV and mean platelet volume (MPV) were determined using the XE-2100 automated haematology analyser (Sysmex, Kobe, Japan) with Sysmex reagents (Sysmex). The normal reference range for RDW in the laboratory of our hospital is 11.6–15%. Serum Amy, creatinine (Cr), blood urea nitrogen (BUN), total protein (TP), albumin (Alb), total calcium (Ca), total bilirubin (TB), glucose (Glu), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities levels were determined with a Hitachi 7600 (Hitachi High-Technologies, Tokyo, Japan) using Roche reagents (Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analyses
RBC, PLT, RDW, Hgb, MCV, MPV, TP, Alb, Glu, Ca and LDH values were normally distributed and reported as the mean±SD. WCC, Cr, BUN, TB, ALT, AST, Amy and AP hospital stay were not normally distributed and were therefore reported as the median (range). The significance of the differences in the haematology and biochemistry results between AP and healthy control groups, patients with SAP and MAP or non-survivors and survivors of patients with AP were determined using a Student t test or Mann-Whitney U test where appropriate. The significance of differences in the haematology and biochemistry results among healthy individuals, SAP and MAP, and among non-survivors of healthy individuals, non-survivors of patients with AP and survivors of patients with AP were determined using one-way analysis of variance or Kruskal-Wallis H test where appropriate. The significance of difference in gender was compared using χ^2 test. The participants were categorised into one of three subgroups depending on their RDW tertiles. To compare the variables between these subgroups, analysis of variance or Kruskal-Wallis H test were used where appropriate. Pearson partial correlation coefficients were computed to present the association between RDW values and other variables. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the values for RDW to predict mortality. The survival curve for the mortality of patients with AP was drawn by Kaplan-Meier analysis according to the cut-off value, and the log-rank test was used to test for differences in survival between the groups. Difference of the area under the ROC curve (AUC) was tested using the z test. The probability cut-off points for the optimal combination of sensitivity and specificity were determined by the Youden index. Statistical analyses were performed with SPSS V.16.0 (SPSS Inc, Chicago, Illinois, USA). All statistical tests were two-tailed with p values <0.05 considered as significant.

RESULTS
Characteristics of study population
Clinical characteristics of MAP, SAP and healthy individuals are summarised in table 1. There was no difference in the gender, serum BUN and PLT count among MAP, SAP and healthy individuals, and there were significant differences in age, serum Cr, TB, ALT, AST, Ca, Amy, TP, Alb, LDH, Glu levels, WCC, RBC count, Hgb, MCV, MPV and RDW at the first test after admission. The RDW was 12.6±0.59 and significantly lower in patients with MAP than in healthy individuals (13.42 ±0.85%, p<0.001); however, the RDW was 14.4±1.06 and significantly higher in patients with SAP than in healthy individuals (13.42±0.85%, p<0.001).

Association of RDW and 3-month mortality in AP
All patients with AP were divided into three groups according to RDW tertiles (group 1: RDW >13.3%, group 2: RDW 12.6–13.3% and group 3: RDW <12.6%), the clinical characteristics of AP according to RDW tertiles are shown in table 2. AP with RDW >13.3% had lower levels of Ca, TP, Alb, Hgb, WCC and RBC count, but higher mortality (6/8). The median hospital stay was 14 days (range 2–75 days); eight patients died during the 3-month follow-up period. The Pearson correlations indicated the correlations between RDW and the age, and biochemical and hematological parameters. In all patients with AP, RDW correlated inversely with Alb (r=−0.254, p=0.009), Ca (r=

Table 1 Clinical characteristics of patients with AP and healthy individuals

	MAP (n=80)	SAP (n=26)	Healthy individuals (n=204)	p Value
Age (years)	48.2±14.7*	60.5±14.5†	48.0±11.7	<0.001‡
Gender (M/F)	41/39	11/15	102/102	0.722§
AP hospital stay (days)	14 (6–75)	14.5 (2–52)		
AP mortality	0	8		
BUN (mmol/L)	4.8 (2–17.5)	4.9 (2.6–15.2)	5.6 (2.7–8.6)	0.208¶
Cr (μmol/L)	52 (35–193)†	59 (37–198)	65 (33–121)	<0.001¶
TB (μmol/L)	18 (6–90)†	17 (9–92)†	13 (6–45)	<0.001¶
ALT (U/L)	35 (7–235)†	33 (15–591)†	18.5 (8–85)	<0.001¶
AST(U/L)	28.5 (12–129)†	31 (15–1989)†	21 (13–45)	<0.001¶
Ca (mmol/L)	2.11±0.24*†	2.03±0.19†	2.31±0.08	<0.001‡
Amy (U/L)	934 (28–3734)*†	506 (28–2277) †	45 (22–110)	<0.001¶
TP (g/L)	59.2±9.05†	58.5±8.00†	74.1±3.5	<0.001‡
Alb (g/L)	36.2±7.15*†	34.0±4.64†	48.3±2.3	<0.001‡
LDH (U/L)	306.8±148.3*†	400.2±207.9†	185.0±32.2	<0.001‡
Glu (mmol/L)	7.30±3.04†	6.83±1.20†	5.21±0.68	<0.001‡
WCC (×10^9/L)	12.2 (2.7–33.9)†	8.9 (4.6–32.0)†	6.3 (4.1–9.5)	<0.001¶
RBC (×10^{12}/L)	4.85±0.67*†	4.15±1.07†	4.59±0.46	<0.001‡
Hgb (g/L)	147±20*	123±29†	144±15	<0.001‡
PLT (×10^9/L)	210±76	181±119†	216±64	0.069‡
RDW (%)	12.6±0.59*†	14.4±1.06†	13.42±0.85	<0.001‡
MCV (fL)	88.60±4.32†	89.6±4.74†	92.82±5.05	<0.001‡
MPV (fL)	11.05±1.27*†	11.58±1.20†	8.82±1.12	<0.001‡

*p<0.05, MAP compared with SAP.
†p<0.05, patients with MAP and SAP compared with healthy individuals.
‡Analysis of variance.
§χ^2 Test.
¶Kruskal-Wallis H test.
Alb, albumin; ALT, alanine aminotransferase; Amy, elevated serum amylase; AP, acute pancreatitis; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; F, female; Glu, glucose; Hgb, haemoglobin; LDH, lactate dehydrogenase; M, male; MAP, mild acute pancreatitis; MCV, mean corpuscular volume; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; SAP, severe acute pancreatitis; TB, total bilirubin; TP, total protein; WCC, white cell count.

−0.226, p=0.021), RBC (r=−0.295, p=0.002) and Hgb (r=−0.407, p<0.001), and directly with age (r=0.236, p=0.015) and LDH (r=0.301, p=0.030).

The non-survivors of AP had lower levels of Ca, TP and Alb, and higher age, BUN, Cr, LDH, WCC and RDW (table 3). The RDW values were significantly different among healthy individuals, non-survivors, and survivors of patients with AP (figure 1). We found that the RDW values were non-survivors>healthy individuals>survivors. To evaluate the values for RDW to predict mortality, ROC curve was drawn (figure 2). The AUC of RDW was 0.846 (95% CI 0.727 to 0.964, p<0.001). We further analysed the PPV and NPV of high RDW, with a cut-off value of 14.2 for RDW. Sensitivity, specificity, positive likelihood ratio (+LR) and negative likelihood ratio (−LR), PPV and NPV of RDW to predict mortality were 75%, 89.8%, 7.35%, 0.28%, 37.5% and 97.8%, respectively. Kaplan-Meier analysis showed an increase in probability of death with high RDW values (log-rank p<0.001; figure 3).

DISCUSSION
RDW is a quantitative measure of variability in the size of circulating erythrocytes with higher values reflecting greater heterogeneity in cell sizes.[17] The high level of

RDW is a novel prognostic marker that may reflect an underlying inflammatory state.[18] AP is an inflammatory disease, and its mechanism is still not completely understood and early pathophysiological events escape clinical observation.[19] Early deaths (within the first week) due to severe AP is generally caused by massive inflammatory responses, which result in multiple organ failure, and late deaths (after 1–3 weeks) is caused by multiple organ dysfunction with infections and sepsis.[19 20] Recent studies found that RDW for predicting mortality were used in cardiovascular diseases, acute dyspnoea and pulmonary diseases.[3–5]

In our study, patients with MAP had significantly lower RDW values compared with healthy individuals, mainly because 80 MAP had lower RDW values in 106 patients with AP compared with healthy participants. The mechanisms that underly this outcome is unclear. Narci et al[21] found a significantly lower RDW level in patients with acute appendicitis compared with those in the control group, and RDW was not correlated with CRP and WCC. They only considered that RDW level in acute conditions may be lower than that in chronic inflammatory diseases, but did not clearly explain the mechanisms why acute appendicitis patients had lower RDW than the healthy group. The reasons why survivors of patients

Table 2 Clinical characteristics among patients with AP according to RDW tertiles

RDW (%)	Group 1 >13.3	Group 2 12.6–13.3	Group 3 <12.6	p Value
n	34	38	34	
Age (years)	55.9±15.1	51.5±14.9	46.2±15.5	0.035*
Gender (M/F)	16/18	28/10	8/26	<0.001†
AP hospital day	16 (2–75)	14 (7–39)	14 (6–29)	0.361‡
AP mortality	6/34	2/38	0/34	0.018†
BUN (mmol/L)	4.9 (2.6–15.2)	5.2 (2–13.5)	4.8 (2.6–17.5)	0.657‡
Cr (μmol/L)	59 (37–198)	63 (35–127)	49 (36–193)	0.07
TB (μmol/L)	18 (10–65)	19 (6–48)	16 (8–50)	0.417‡
ALT (U/L)	34 (15–591)	38 (7–234)	27 (7–235)	0.208‡
AST (U/L)	31 (12–1989)	27 (12–111)	28 (14–72)	0.338‡
Ca (mmol/L)	2.03±0.21	2.05±0.28	2.19±0.16	0.008‡
Amy (U/L)	506 (28–2277)	948 (28–3734)	1002 (55–2708)	0.051‡
TP (g/L)	57.5±8.8	57.7±7.8	62.2±9.2	0.04*
Alb (g/L)	33.2±5.6	34.6±6.0	39.2±7.0	<0.001*
LDH (U/L)	361.3±194.1	392.2±150.9	254.1±138.5	0.041*
Glu (mmol/L)	7.02±1.66	6.71±2.57	7.85±3.57	0.269*
WCC (×10⁹/L)	9.3 (4.6–32)	15.1 (4.5–33.9)	11.1 (2.7–23.1)	0.012‡
RBC (×10¹²/L)	4.32±1.00	5.04±0.70	4.62±0.62	0.001*
Hgb (g/L0	128±28	152±20	144±20	<0.001*
PLT (×10⁹/L)	183 (54–540)	212 (93–336)	213 (85–402)	0.052‡
MCV (fL)	88.54±5.01	88.52±4.84	89.54±3.18	0.550*
MPV (fL)	11.56±1.23	11.08±1.15	10.88±1.38	0.087*

*Analysis of variance.
†χ^2 Test.
‡Kruskal-Wallis H test.
Alb, albumin; ALT, alanine aminotransferase; Amy, elevated serum amylase; AP, acute pancreatitis; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; F, female; Glu, glucose; Hgb, haemoglobin; LDH, lactate dehydrogenase; M, male; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; TB, total bilirubin; TP, total protein; WCC, white cell count.

with AP had lower RDW than the healthy participants may be that RBC of most survivors was damaged and bone marrow did not secrete new RBC into the peripheral circulation in early inflammatory phase. In our study, there was no difference in the serum BUN, Hgb levels and PLT count between the MAP and healthy individuals (table 1). Possibly because MAP in 106 patients with AP had the BUN, Hgb levels, RBC and PLT count close to healthy individuals; however, the eight non-survivors of AP had significantly higher BUN compared with survivors, and had lower levels PLT count, and higher Hgb and RBC count although there was no significant difference (table 3). We also found that among AP groups according to RDW tertiles, group 1 with the highest RDW values had highest mortality (figure 1); the non-survivors of patients with AP had highest RDW values compared with healthy individuals and survivors of patients with AP (figure 1), thus patients with AP with high RDW had a high mortality. ROC curve analysis indicated that sensitivity and specificity of RDW to predict mortality were 75% and 89.8%. Kaplan-Meier analysis showed that a high RDW value had a high probability of death. Thus, we speculated that RDW values were an important factor that influences the disease progression and associated with increased mortality in patients with

**Table 3** Significant laboratory parameters in survivors and non-survivors of AP

|	Non-survivors	Survivors	p Value
n	8	98	
Age (years)	67.3±11.8	49.9±15.0	0.002*
Gender (M/F)	4/4	48/50	0.956†
BUN (mmol/L)	8.8 (8.6–13.5)	4.6 (2.0–17.5)	<0.001‡
Cr (μmol/L)	102 (59–198)	52 (35–193)	0.001‡
Ca (mmol/L)	1.87±0.24	2.11±0.23	0.004*
TP (g/L)	53.2±3.78	59.5±8.9	0.028*
Alb (g/L)	30.7±2.87	36.0±6.7	0.006*
LDH (U/L)	494.8±25.17	304.5±136.5	0.003*
WCC (×10⁹/L)	18.4 (9.3–20.2)	12.7 (2.7–33.9)	0.035‡
RDW (%)	14.2±0.72	12.98±1.04	0.002*
RBC (×10¹²/L)	4.97±1.15	4.65±0.81	0.166*
Hgb (g/L)	145±31	141±24	0.609*
PLT (×10⁹/L)	176 (112–202)	191 (54–540)	0.282‡

*Student t test.
†χ^2 Test.
‡Mann-Whitney U test.
Alb, albumin; Amy, elevated serum amylase; AP, acute pancreatitis; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; F, female; Glu, glucose; Hgb, haemoglobin; LDH, lactate dehydrogenase; M, male; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; TP, total protein; WCC, white cell count.
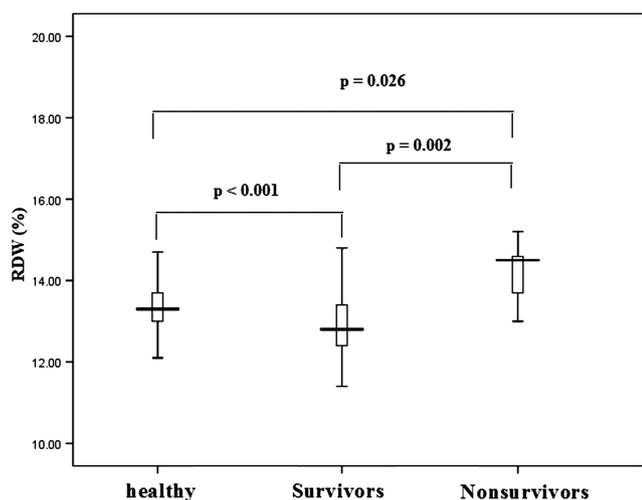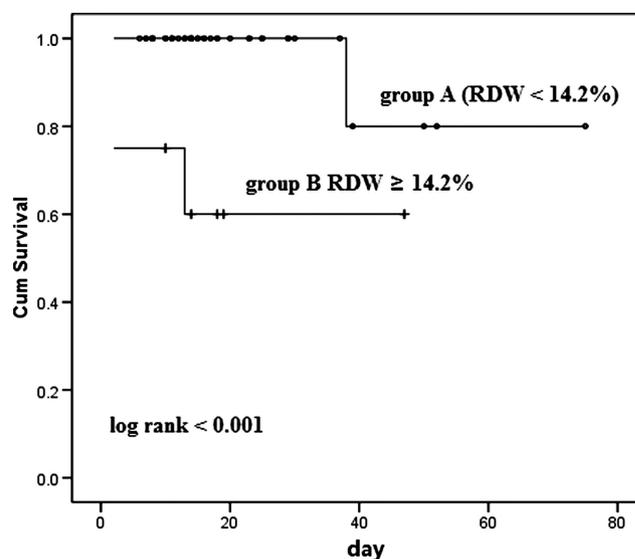
Figure 1 Red cell distribution width (RDW) values of healthy individuals, non-survivors and survivors of patients with acute pancreatitis. RDW values are significantly different among three groups (one-way analysis of variance, p<0.001).

AP. As far as we know, only one study by Şenol et al[22] described that RDW on admission was a predictor of mortality in Turks with AP.

The mechanisms underlying the association between RDW and mortality in AP are unclear. Some studies indicated that RDW may also be related with inflammation, and not only with anaemia.[3–5] Moreover, RDW has been found to be strongly associated with inflammatory markers (eg, CRP or erythrocyte sedimentation rate) in a large cohort of unselected outpatients.[18] Elevated levels of inflammatory cytokines and alterations in iron metabolism together with inflammatory
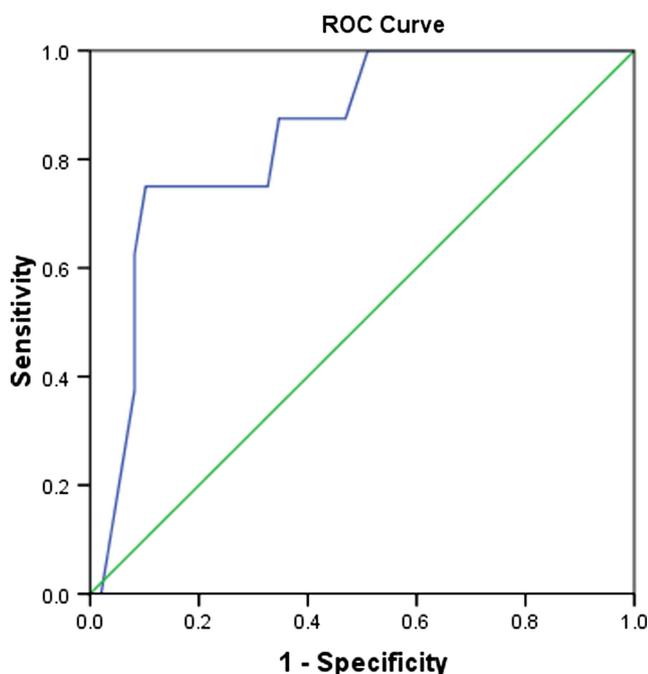
Figure 2 Receiver-operating characteristic (ROC) curve analysis for mortality prediction.

Figure 3 The survival curve for the mortality of patients with acute pancreatitis (RDW, red cell distribution width).

states may decrease endothelial nitric oxide production, which is known to stimulate the proliferation of erythroid progenitor cells, and be implicated in the development of anaemia and change of RDW.[18 23] However, after adjustment for CRP, Zhang et al[24] found that RDW was independently associated with in-hospital mortality (OR 1.1, p=0.002). On the basis of a multi-ethnic population, Veeranna et al[25] also found that RDW (HR 1.26, p<0.001) may be considered a stronger biomarker for coronary heart disease mortality than CRP (HR 1.18, p=0.077), after further analysis of mortality prediction in categorised CRP subgroups, RDW remained a significant predictor in the CRP subgroups ($\leq$ and >3 mg/L).

A few limitations warrant consideration. First, we did not investigate the causes of elevated RDW values in non-survivors of patients with AP. Second, our study was a small sample size and single-centre study. Therefore, future large-size and multicentre studies are required to further clarify whether RDW is a predictor in patients with AP.

In conclusion, our results indicated that the RDW values were non-survivors of patients with AP>healthy individuals>survivors of patients with AP; patients with AP with the highest RDW tertiles had the highest mortality and the non-survivors of AP had higher RDW values when compared with survivors, and a cut-off value of 14.2 for RDW to predict mortality.

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