 doi:10.20944/preprints202211.0097.v1

Article

Disease Severity and Prognostic Nutritional Index (PNI), C-Reactive Protein (CRP), and Red Blood Cell Distribution Width (RDW) in Acute Pancreatitis

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ABSTRACT: Background: Acute pancreatitis is a common emergency. Morbidity control requires early detection of disease severity. **METHODS:** A total of 131 AP patients were analyzed retrospectively. Patients were divided into two groups mild AP (MAP: Ranson score <3) and severe AP (SAP: Ranson score ≥3), according to Ranson's criteria. Demographic data, hospitalization duration, PNI, CRP, and RDW levels were compared. Any p-value below 0.05 ($p<0.05$) was accepted as statistically significant. **RESULTS:** Study included 67 (51.15%) males and 64 (48.85%) females. The age average was 59.74 (19-90) years. 95 (72.52%) patients had MAP, and 36 (27.48%) patients had SAP. Mean hospitalization time, PNI, and CRP differed significantly between the two groups ($p=0.010$, $p<0.05$, $p<0.05$, respectively). The RDW ($p=0.380$) level difference was insignificant. For SAP prediction; the sensitivity, specificity and cut-off value according to Ranson code cut-off point for PNI were determined as 80.0% (95% CI:54.8-85.8), %72.2 (95% CI:70.5-87.5) and ≤45.6 (gr/L) + (mm^3), respectively, and 94.7% (95% CI:57.8-87.9), %75.0 (95% CI:88.1-98.3) and >105,1 mg/L, respectively for CRP. **CONCLUSION:** PNI and CRP values (but not RDW values) were compatible with the disease severity determined by the Ranson criteria.

Keywords: Acute pancreatitis; prognostic nutritional index; C-reactive protein; red cell distribution width; Ranson's criteria; severity

INTRODUCTION

Acute pancreatitis (AP) is a rapidly developing inflammatory disease of the pancreas, which is usually diagnosed after detecting elevated pancreatic enzyme levels in the blood and radiological examinations in patients with severe acute upper abdominal pain. A significant part of the patients who refer to the emergency clinic is AP patients (1, 2). The most common cause for emergency department referrals is AP among gastrointestinal diseases. Two crucial causes that constitute 2/3 of the cases are gallstones and chronic alcohol use in the etiology of AP. Some studies have reported that biliary AP prevalence is higher, and it has been reported that biliary AP is more severe with higher mortality than alcohol-induced AP (3). AP is a disease that may range in severity from a mild self-limiting illness to progressive multi-organ failure. Severe AP (SAP) is 10% to 20% of the patients with AP; these patients are associated with severe, progressive disease and poor prognosis (4, 5). Mortality ranges from 3% in patients with interstitial edematous pancreatitis to 17% in patients who developed pancreas necrosis (6).

Currently, enzyme levels include amylase, lipase, trypsin, trypsinogen activation peptide (TAP), urinary and serum trypsinogen-2, phospholipase, carboxypeptidase are used to determine or predict the severity of AP. Furthermore, immune activation markers such as AP are associated with elevations in C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor (TNF) are used (7, 8). In addition, some scoring

 doi:10.20944/preprints202211.0097.v1

systems are used to help determine AP's severity and prognosis. Ranson's criteria, acute physiological assessment and chronic health assessment (APACHE) II, bedside index of severity in acute pancreatitis (BISAP), and Balthazar score are some of the most commonly used methods (9, 10).

Ranson's criteria are one of the well-known scoring systems that have been commonly used for a long time to determine severity in AP. Ranson's criteria consist of 11 parameters. Five factors are evaluated at referral, and six are assessed within the next 48 hours. Mortality increases along with increased score; when the score is below 3, the mortality is between 0 and 3%; when the score is at and above 3, the mortality rate is between 11% and 15%, and when the score is at and above 6, the mortality rate was reported as 40% (11, 12).

CRP was reported as highly sensitive and specific for SAP. The test cost of CRP is cost-effective and such tests may be easily obtained (13-15). There is increasing evidence that systemic inflammatory response is associated with poor survival in various diseases, including malignancies. Inexpensive and ready-made laboratory tests that may be used routinely, such as NLR (neutrophil-lymphocyte ratio), MPW (mean platelet volume), RDW (red cell distribution width), PLR (platelet lymphocyte ratio), LMR (lymphocyte monocyte ratio) have been investigated as a biomarker of systemic inflammation. The relationships of these biomarkers with the severity, treatment response, and prognosis of various diseases such as malignancies, rheumatological diseases, cerebrovascular diseases, cardiovascular diseases, and kidney diseases have been investigated, and essential relationships have been identified (14, 16).

In our literature search, we found a study with PNI to predict the severity of acute pancreatitis; in that study, PNI was an essential indicator of severity, but the severity of pancreatitis was not determined according to the Ranson score (17). First, we wanted to investigate CRP, RDW, and PNI measures to predict pancreatitis severity, which we determined according to Ranson's score, which is well-known and frequently used by most clinicians.

MATERIAL AND METHODS

Patients and Study Design

Our study was conducted on 131 adults over 18 years of age who were followed up by the gastroenterology and internal diseases clinics of Istanbul Uskudar State Hospital, department of internal medicine, gastroenterology clinic due to the diagnosis of AP with any etiology between October 2016 and December 2021. Demographic, clinical, examination, laboratory, imaging, and hospitalization follow-ups of the patients were reviewed retrospectively through the hospital automation system and patient files. Patients under 18, patients followed in the intensive care unit, patients with acute/chronic infection and acute/chronic inflammation not associated with local and systemic involvement of AP, and patients with malignancies, including pancreatic cancer, were excluded from the study.

According to the AP severity classification according to the most recently revised Atlanta criteria, AP severity was divided into three; mild (AP is characterized by the absence of organ failure and the absence of local or systemic complications), moderately severe (AP is characterized by transient organ failure in the lack of permanent organ failure or the presence of local or systemic complications) and severe AP (AP is characterized by persistent organ failure) (23). Unlike the revised Atlanta criteria, we divided our patients into two groups moderate AP (MAP: score <3) and severe AP (SAP: score ≥3), which we determined according to Ranson scores (24).

The age, hospitalization period, CRP (normal range:0-5 mg/L) at referral, RDW (%), and prognostic nutritional index (PNI= 10 x albumin (gr/L) + 0,005 × total lymphocyte

 doi:10.20944/preprints202211.0097.v1

count (mm^3)) measurements of both groups were compared. The association of these laboratory results with the disease severity determined by Ranson's criteria was investigated.

Approval was obtained from the Ethics Board of Zeynep Kamil Women and Children Disease Training and Research Hospital (24.11.2021, Decision No: 180)

Statistical Analysis

The SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc statistics program were used for data evaluation. Descriptive statistics (mean, standard deviation, number, and percentile) were given for categorical and continuous variables in the study. Furthermore, the homogeneity of the variances, one of the prerequisites of the parametric tests, was checked with the "Levene" test. The normality assumption was analyzed by "Shapiro-Wilk" test. When the differences between the two groups wanted to be evaluated, the "Student's t-Test" was used if the parametric test prerequisites were met; and if they were not, the "Mann Whitney-U test" was used. The "Roc Curve" analysis method was used to compare the diagnostic performances of two or more diagnostic or laboratory tests. The associations between categorical variables were analyzed through Fisher's Exact Test and Chi-Square test. When the expected frequencies were below 20%, an assessment was performed through the "Monte Carlo Simulation Method" to include these frequencies in the analysis. Any p-value below 0.05 ($p<0.05$) was accepted as statistically significant.

RESULTS

One hundred and thirty-one patients with AP were included in the study. The age average of the patients was 59.74 (19-90); the patients included 67 (51.15%) males and 64 (48.85%) females. The review of etiologies of AP revealed that 65 (49.62%) patients had biliary AP, whereas 66 (50.38%) patients had non-biliary AP. The average hospitalization period of the patients was 7.40 (0-54) days. In our study, no patients were admitted to the intensive care unit or died. The Ranson's score average of the patients was 2.20 (0-6). Mean RDW measurements of all patients was 14.67% (11.68-23.90), mean CRP value was 71.60 mg/L 0.09-463.8), mean PNI value was detected as 41.87 gr/L + mm^3 (28.15-60.5). The patients were first divided into two groups, MAP (score <3) and SAP (score ≥3), according to Ranson's criteria. It was detected that 95 (72.52%) patients had MAP, and 36 (27.48%) patients had SAP. The age, hospitalization period, PNI, CRP, and RDW were analyzed in MAP and SAP groups; the differences and associations between the two groups were reviewed statistically (Table 1). No significant difference was detected between both groups for age and RDW averages ($p>0.05$). A significant difference was detected between the groups in terms of mean hospitalization period, CRP, and PNI averages ($p<0.05$). PNI was higher in the MAP group; however, hospitalization period and CRP averages were higher in the SAP group. The determination of limit values for CRP parameters was statistically significant as a result of cut-off scores, AUC (area under ROC curve) value, sensitivity, specificity, and statistical significance according to Ranson's code value ($p<0.05$). The specificity and sensitivity for PNI was 80.0% (95% CI: 54.8-85.8) and 72.2% (95% CI: 70.5-87.5), respectively; the limit value according to Ranson's code cut-off point was ≤45,6 gr/L + mm^3; the specificity and sensitivity for CRP parameter was 94.7% (95% CI:57.8-87.9) selectivity and 75.0% (95% CI: 88.1-98.3) the limit value according to Ranson code cut-off point was >105,1 mg/L (Table 2.). The area under the curve (AUC) was found to be 0.917 (91.7%) for CRP and was statistically significant ($p<0.001$). This value has a strength of 91.7% in distinguishing CRP from the Ranson score, and it was able to distinguish MAP and SAP patients with a probability of 91.7% (Graphic 1). The area under the curve was found to be 0.818 (81.8%) for PNI, and it was statistically significant ($p<0.001$). This value has a strength of 81.8% in distinguishing CRP from the Ranson score, and it was able to distinguish MAP and SAP patients with a probability of 81.8% (Graphic 2). The area under

 doi:10.20944/preprints202211.0097.v1

the curve was 0.578 (57.8%) for RDW, which was not statistically significant (p=0,1693, Graphic 3).

Table 1. Comparison of demographic, clinical, and laboratory values between moderate and severe acute pancreatitis groups.

	Moderate Acute Pancreatitis	Severe Acute Pancreatitis	p
Age (years)	58.62 ± 18.92	62.69 ± 17.71	0.270
RDW (%)	14.57 ± 2.21	14.94 ± 1.95	0.380
Hospitalization duration (days)	6.03 ± 4.59	11 ± 10.52	0.010*
CRP (mg/L)	30.62 ± 41.37	179.74 ± 110.38	0.001*
PNI ((g/L) + (mm^3))	48.95 ± 5.65	41.39 ± 6.28	0.001*

*Student's t Test.
n:number, RDW: red cell distribution width, CRP: C-reactive protein, PNI: prognostic nutritional index, any p-value below 0.05 (*: p<0.05) was accepted as statistically significant.

Table 2: ROC analysis according to Ranson's code cut-off.

	Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	AUC	p
CRP	>105.1	75	57.8 - 87.9	94.74	88.1 - 98.3	14.25	5.9 - 34.1	0.26	0.1 - 0.5	0.917	<0.0001
PNI	≤45.6	72.22	54.8 - 85.8	80	70.5 - 87.5	Mar.61	2.3 - 5.7	0.35	0.2 - 0.6	0.818	<0.0001
RDW	>14.6	52.78	35.5 - 69.6	64.21	53.7 - 73.8	Oca.47	1.0 - 2.2	0.74	0.5 - 1.1	0.578	0.1693

AUC: area under the ROC curve, RDW: red cell distribution width, CRP: C-reactive protein, PNI: prognostic nutritional index, any p-value below 0.05 (p<0.05) was accepted as statistically significant.

DISCUSSION

A significant portion of patients with abdominal pain presenting to emergency services are patients with AP. Approximately 15% to 25% of the patients diagnosed with AP develop moderate or severe AP. A large epidemiological study conducted in the United States reported that the death rate from AP decreased from 12% to 2% between 1988 and 2003 (18). Despite advances in diagnostic methods, new treatment approaches, and improvements in intensive care conditions, the mortality rate in AP is still high. Multiple organ failure and infectious necrosis are the two most important factors increasing mortality (18-20). Predicting AP severity early may help determine the patients at increased risk of morbidity and mortality. It may be helpful for appropriate and early referral of patients from the emergency room to clinics and intensive care units and for specific interventions. Several models have been developed to predict AP severity based on clinical, laboratory, and radiological risk factors, severity rating scores, and serum markers. Immune markers such as CRP, IL-6, IL-8, IL-10, TNF, scoring systems such as Ranson's criteria, APACHE-II, BISAP, sequential organ failure assessment (SOFA), Atlanta, and Balthazar have been used to predict AP severity and prognosis, enzyme levels such as amylase, lipase, trypsin, TAP, phospholipase, carboxypeptidase; these were investigated in studies, and many of them are related to disease severity and prognosis (21, 22).

Ranson scoring is widely used in emergency services, internal medicine, general surgery, and gastroenterology clinics to predict disease severity and prognosis (9). Ranson's criteria may be considered a relatively complicated scoring system that includes many laboratory parameters and evaluation at the time of admission and after 48 hours; for this reason alone, other classification systems or biomarkers have been investigated. We have examined PNI, CRP, and RDW measurements as easily accessible, fast, and inexpensive laboratory tests that may predict MAP and SAP groups, which are separated according to Ranson's criteria, with higher specificity and sensitivity. We may be measured in blood samples that can be taken in every health center. We found in our study that the PNI and CRP measurement results were significantly different between MAP and SAP patients (p<0.001, Table 1). According to ROC analysis, PNI and CRP could correctly discriminate between MAP and SAP patients by 81.8% and 91.7%, respectively, through the Ranson score (Graphics 1 and 2). According to the ROC analysis, the sensitivity for CRP was 94.7%

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and 75.0%, respectively, with a cut-off value above 105.1 mg/L according to Ranson's code cut-off value. The specificity and sensitivity for PNI were 80.0% and 72.2%, with a limit value of ≤45,6 g/L + mm^3 (Table 2). According to these results, CRP and PNI values, especially CRP, are precious in predicting SAP severity according to Ranson's criteria. Furthermore, we found that the number of hospitalization days was significantly different in MAP and SAP patients, and SAP patients had longer hospitalization days; however, this is a criterion based on post-discharge ($p<0.010$, Table 1). We did not detect that RDW measurements have not revealed a significant difference for MAP and SAP patients (Table 1, Graphic 3).

Many biomarkers such as PNI, CRP, and RDW have been investigated as diagnosis, treatment response, and prognostic indicators in many different diseases such as malignancies, many infections and inflammations, rheumatological diseases, cardiovascular diseases, cerebrovascular diseases, and kidney diseases (16, 21-23). CRP is one of the acute phase reactants produced by the liver in response to IL-1 and IL-6. In AP, the sensitivity, specificity, positive predictive, and negative predictive value for SAP of CRP measurements above 150 mg/L at 48 hours were reported to be 80%, 76%, 67%, and 86%, respectively. Our study found the specificity and sensitivity rates for SAP as 94.7% and 75.0%, respectively, with measurement values above 105.1 mg/L for CRP (Table 2, Graphic 1). Similar results have been reported in many other studies. RDW is a low-cost, reliable whole blood analyzer representing red cell distribution volume. It may be quickly and measured. RDW is a valuable inflammatory marker in many diseases, such as cardiovascular diseases, renal failure, chronic inflammations, sepsis, and malignancies, and has been associated with mortality and extended hospital stays (23-25). Significant results of RDW measurements were reported as an early indicator of AP severity and mortality in two clinical studies conducted in our country (26, 27). Similar to our and Yilmaz EM et al.' study, it was found that RDW measurements according to Ranson's criteria did not help predict SAP (7). In clinical studies, especially in cancer patients, patients' nutritional status and immunity were associated with Alan's prognosis(28, 29). PNI is a measurement that reflects the immunological and nutritional status of the patient, calculated through albumin and absolute lymphocyte count. Studies have been conducted recently to demonstrate the prognostic importance of PNI in many cancer types, such as esophageal, colorectal, and gastric cancer (30, 31). The only study on the appearance of SAP in the patients with AP and PNI measurements as a prediction for mortality was conducted by Li Y. et al.; they reported that lower PNI values at baseline were predictive of SAP formation ($p<0.001$), and they were also significant in predicting mortality ($p=0.011$, HR=2.641). The value of 41.1 was cut off deal (14)(2. Pian G et al., in their study, determined PNI according to the severity classification determined by a non-Ranson's classification, 40,625 value and 84.8% and 74.1% sensitivity in SAP estimation and specificity, respectively (17). In this study, a significant correlation was found between the lower PNI values measured at the beginning and the development of SAP ($p<0.001$), and the cut-off value was determined as 45.6, and measurements below this value were found to be specific and sensitive for SAP prediction (Tables 1 and 2, Graphic 2). In the same study, higher initial RDW and CRP values were associated with SAP and mortality. In our study, no patients developed mortality; the reason is that some SAP patients were referred to tertiary care hospitals and intensive care units.

Strengths and Limitations

The main limitations of the study are the relatively small sample size,

It is a retrospective study, and the applicability of the results to the general population is limited.

 doi:10.20944/preprints202211.0097.v1

Conclusion

In conclusion, we evaluated the relationship between CRP, RDW and PNI measured at admission in patients with mild and severe AP, which we determined according to Ranson's criteria. Our study revealed that AP patients were susceptible and specific in estimating SAP patients determined by Ranson's standards, with lower baseline PNI measurements (<45.6 g/L + mm^3) and higher CRP measurements (>105.1 mg/L). PNI and CRP values, easily measured in the laboratories of almost every health center, can be cheap, simple, practical, and safe in estimating the severity of the disease in patients with AP. In our literature search, we saw a study on overall survival in patients with AP due to PNI and a survey that predicted and determined the severity of the disease with a non-Ranson classification. Our work is valuable in this sense. However, there is a need for multicenter and prospective studies with a much larger number of patients to support this idea.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

The authors received no financial support for this article's research and authorship.

Disclosure of conflict of interest: The authors declare no conflict of interest in preparing this article.

The authors declared no conflicts of interest concerning the authorship and publication of this article. The authors have no commercial associations or sources of support that might pose a conflict of interest. The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g., employment, consultancies, stock ownership, and honoraria).

Consent: Written consent was obtained from each patient to use their hospital data. The Ethics Board of Zeynep Kamil Women and Children Disease Training and Research Hospital obtained the study approval.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions: We declare that each author has made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in work; have drafted the work or substantively revised it; has approved the submitted version; agrees to be personally accountable for the author's contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

 doi:10.20944/preprints202211.0097.v1

Figures and the legends

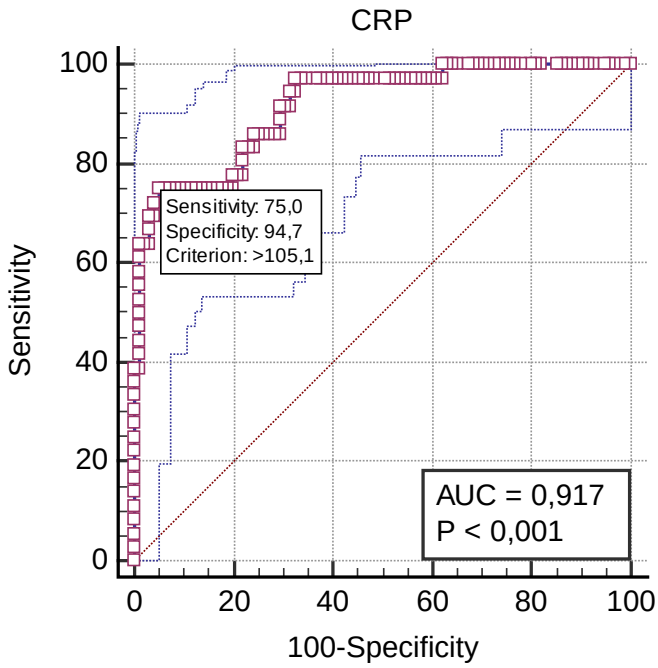

Figure 1. C-reactive protein ratio cutoff ROC curve according to Ranson value (ROC: Receiver operating characteristic, CRP: C-reactive protein).

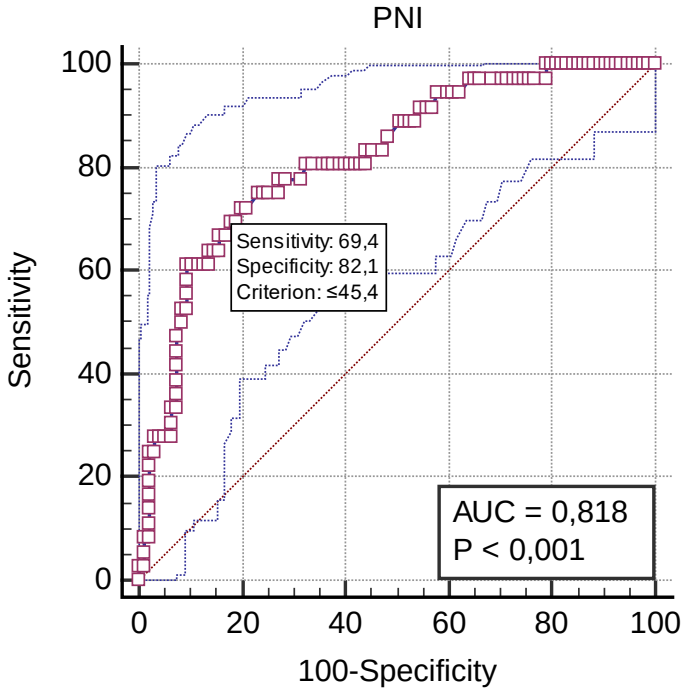

Figure 2. Prognostic nutriotinel index ratio cutoff ROC curve according to Ranson value (ROC: Receiver operating characteristic, PNI: prognostic nutritionel index).

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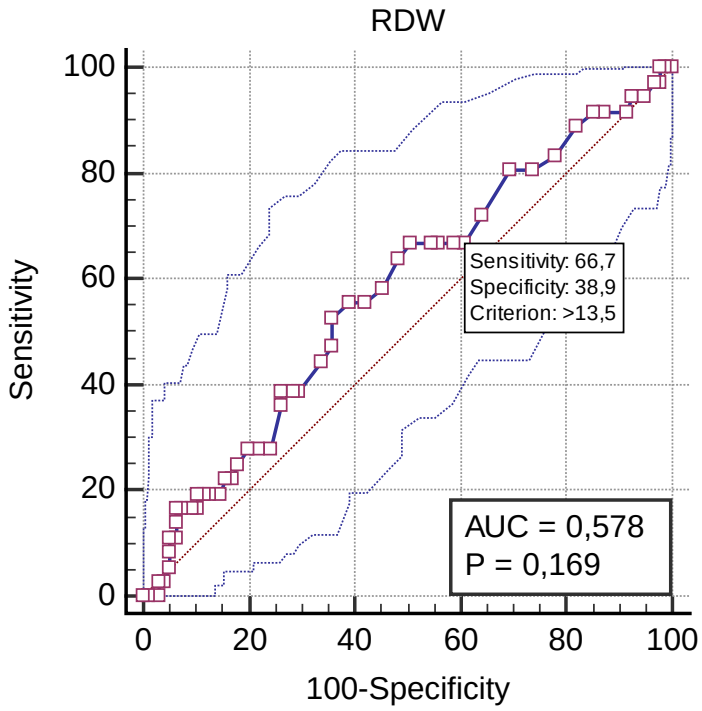

Figure 3. Red cell distribution width ratio cutoff ROC curve according to Ranson value (ROC: Receiver operating characteristic, RDW: red cell distribution width).

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