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**Red cell distribution width to platelet ratio: New and promising prognostic marker in acute pancreatitis**

Çetinkaya *et al*. RDW to platelet ratio, acute pancreatitis

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**Abstract**

**AIM:** To evaluate the accuracy of red cell distribution width (RDW) to platelet ratio (RPR) for prediction of in-hospital mortality in acute pancreatitis (AP).

**METHODS:** Between January 2010 and June 2012 a total of 102 patients with acute pancreatitis were recruited to the study. In this retrospective cohort study, for all subjects demographic data on hospital admission, AP etiology, co-morbid diseases, organ failure assessment, laboratory parameters, and length of hospital stay were examined. Additionally we used the non-invasive prediction method in addition to the RPR to evaluate the disease severity. Multivariate logistic regression analyses were used to evaluate the impact of RPR obtained on hospital admission for predicting mortality.

**RESULTS:** Male-female ratio (59/43) was 1.37 with a median age of 56.5 years (17-89 years). In both univariate and multivariate analyses, RDW and RPR were presented as an independent significant variable on admission to predict the mortality. The RPR obtained on hospital admission was persistently higher among non survivors than survivors (*P* < 0.0001). Median RPR was 0.000087 in the non survivor group and 0.000058 in the survivor group. RPR with a cutoff value of 0.000067 presented an area under the curve of 0.783 (95%CI: 0.688-0.878) in Receiver operating characteristic curves and predicted the mortality approximately in 80% of the patients.

**CONCLUSION:** We identified RPR as the valuable, novel laboratory test for predicting mortality in AP.

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**Key words:** Acute pancreatitis; Red cell distribution width; Red cell distribution width to platelet ratio

**Core tip**: Although a majority of patients with acute pancreatitis have a mild course of the disease, severe forms require more attention due to their high morbidity and mortality. Several single- and multi-parameter scoring systems including laboratory parameters, physiological, and radiologic assessments have been described to evaluate disease severity. Sometimes it is not clinically practice to use these scoring systems for evaluation therefore an easy to use and useful method is needed for predicting mortality.

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**INTRODUCTION**

Acute pancreatitis (AP) is an acute inflammatory disease, and one of the most frequent gastrointestinal causes of hospital admission. The incidence of AP is 150-420 cases per million in the United Kingdom, and 330-430 cases per million in the United States[1]. The majority of patients have mild, self-limited disease, however approximately 20% of patients have a severe form[2]. AP has three phases; the first phase is characterized by enzymatic activation and cellular injury that leads early symptoms. In the second phase, pro-inflammatory and anti-inflammatory mediators play a role in systemic inflammatory response, intrapancreatic inflammatory reaction occurs, and the third phase involves the complications of AP[1]. The early assessment of disease severity to estimate the complications and even organ failure is fundamental: approximately 23% of the deaths attributable to AP occur in the first 3 days and 53% within the first week [3].

 There are have been described several single- and multi-parameter predictors to evaluate the severity of the disease. Some scoring systems such as Ranson, Glasgow and APACHE II can provide valuable clues to evaluate severity and mortality of AP. Also, in several studies some biological markers such as elevated C-reactive protein, elevated creatinine, high blood glucose and hemoconcentration on admission have been used to predict mortality [4].

 Complete blood count is a laboratory test frequently used in clinical practice and consists of white blood cell, red blood cell, platelet counts and their morphological indices such as red cell distribution width (RDW). RDW measures size variability of erythrocytes. As it is widely used to differentiate the etiology of anemia, in previous studies RDW was shown to be a useful marker for celiac disease, colon cancer, and acute coronary syndromes[5,6]. Also, it was shown that hemostatic disorders ranged from hipercoagulopathy to disseminated intavascular coagulation appear in the acute phase of AP and are related to disease severity[7]. In a recent study for predicting hepatic fibrosis stages in patients with chronic Hepatitis B, Chen *et al*[8] used the RDW to platelet ratio (RPR). By using these two parameters that can be calculated easily, they stated that liver biopsy necessity for these patients will be reduced. Based on this study, as this ratio reflects inflammation severity, we aimed to evaluate the severity of patients with AP with RPR on hospital admission.

## **MATERIALS AND METHODS**

## A total of 102 patients with AP were recruited in the study between January 2010 and June 2012. AP was diagnosed with typical physical examination findings associated with a plasma amylase level greater that 500 IU/L, and radiologic verification of the disease by ultrasonography and/or abdominal tomography. In this retrospective study, for all subjects demographic data on hospital admission, etiology of pancreatitis, organ failure, co-morbid diseases, length of hospital stay, and the following laboratory measures such as serum amylase, C-reactive protein, complete blood count, serum electrolytes, serum enzymes associated with cholestasis, serum hepatic and renal function tests, bilirubin levels, fasting blood glucose, lactate dehydrogenase, capillary gas analysis (partial pressure of oxygen, pH, and base excess), were analyzed from each patient records. Also we calculate RPR by using the following index. RPR = RDW (%)/platelet (109/L)[8].

## ***Statistical analysis***

Data are presented as median value (interquartile range), and Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality. The prognostic factors that influence the mortality in univariate analyses were determined with Mann-Whitney *U* test and *χ*2 test. Factors identified as significant in univariate analyses were included into multivariate logistic regression analysis. Receiver operating curve analyses were used to evaluate the mortality predictive performances and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) measures of each significant variable with different cutoff values.

All statistical procedures were performed with SPSS 15.0 (SPSS Inc, Chicago, Illinois). *P* < 0.05 was considered to be significant.

**RESULTS**

In this retrospective cohort study, 59 female and 43 male patients were included with a median age of 56.5 years (17-89 years). AP etiology was biliary stones in 75 and alcohol in 37 of the patients. Local complications during follow-up were respectively; 15 pseudocysts, 4 pancreatic abscesses, and 6 necrotizing pancreatitis. A total of 13 patients were died after a median of 6 d of hospitalization (1-88 d). The demographic and clinical features of the patients were summarized in [Table 1](http://www.sciencedirect.com/science/article/pii/S0735675712006547#t0005).

Age, WBC count, platelet count, calcium level, BUN level, RDW, RPR and albumin level were the significant variables in univariate analysis that influence the survival rates of AP on admission. Variables on admission found to be significant in univariate analyses were entered into multivariate analyses. In both univariate and multivariate analyses, RDW and RPR were presented as independent significant variables on admission to predict the mortality ([Table 1](http://www.sciencedirect.com/science/article/pii/s0735675712006547%22%20%5Cl%20%22t0005)). The RPR obtained on hospital admission was persistently higher among non survivors than survivors (*P* < 0.0001). Median RPR was 0.000087 in the non survivor group and 0.000058 in the survivor group. We further analyzed the PPV (26.67%, 95%CI: 14.6-41.9) and NPV (96.39%, 95%CI: 89.7-99.2) of high RPR. RPR with a cutoff value of 0.000067 presented an area under the curve of 0.783 (95%CI:0.688-0.878) in Receiver operating characteristic curves ([Figure 1](http://www.sciencedirect.com/science/article/pii/S0735675712006547#f0005)) and predicted the mortality approximately in 80% of the patients (sensitivity, 80.00%, 95%CI: 51.91-95.43; specificity, 70.08%, 95%CI: 61.50-78.97; +LR: 2.74; -LR: 0.28).

**DISCUSSION**

Although a majority of patients with acute pancreatitis have a mild course of the disease, severe forms require more attention due to its high morbidity and mortality. The rate of mortality in severe acute pancreatitis may be as high as 25%[4]. So early diagnosis and management is fundamental in order to maximize organ support and to prevent irreversible organ dysfunction.

 There are several simple predictors to evaluate the severity of the disease. Several scoring systems such as Ranson, Glasgow and APACHE II are mainly useful in clinical practice. These scoring systems are expected to provide valuable clues in the assessment of the severity. However, a meta-analysis of 110 studies demonstrated that Ranson score proved insufficient data over predicting the severe form of disease with lower positive and negative predictive values[9]. Also, it has been argued that SIRS on admission have been assessed the severity of the disease more accurate than APACHE II scoring system[10]. In the present study the performance of RPR was compared with Ranson criteria, and found to be more sensitive than this severity score.

 It was published that to recognize organ dysfunction earlier, some biological markers could be used. In a large observational cohort study, serial BUN measurements of AP patients on admission, 24 and 48 h have been described as the most predictive marker of in-hospital mortality compared to the serial hemoglobin/hematocrit measurements. Authors also noticed that extent of BUN increase was demonstrated as a single accurate prognostic marker which highly was associated with the risk of mortality[11]. In another study hemoconcentration due to fluid loss in a third space was mentioned as a single reliable severity predictor of AP. Patients presented with hematocrit level below 44%-47% on admission and patients not responding to resuscitation within 24 h have the risks to develop necrotizing pancreatitis, so patients with hemoconcentration should be monitorized in intensive care unit with exclusive attention on aggressive fluid resuscitation. Hemoconcentration usually correlates with pancreatic necrosis and absence of hemoconcentration suggests a benign course of the disease[12,13]. Also there are many other serum markers studied for predicting the severity of the disease such as C-reactive protein, urinary trypsinogen activation peptide, procalcitonin, polymorphonuclear elastase, interleukins-1, 6, 8 and 10, antithrombin III (AT III), platelet activating factor[14]. In which of these markers have some limitations in clinical use. For example C-reactive protein and procalcitonin are non-specific and require time for results. Also urinary trypsinogen activating peptide, the specific marker of protease activation, is not currently available[11].

 Inflammatory mediators have a pivotal role in the pathogenesis of AP, also influence hemostasis and lead to coagulation abnormalities. These range from intravascular thrombosis to disseminated intravascular coagulation. Platelet activating factor is an inflammatory mediator and plays a role in the early stages, as it activates platelets, neutrophils, mast cells and amplifies other cytokines production. Also another important factor in the coagulation cascade known as tissue factor induces coagulopathy and leads to reduced platelet count, fibrinogen and AT III levels[7]. In a study of 27 patients with acute pancreatitis it was shown that platelet counts, prothrombin levels were decreased[15] while in another study it was found that plasma prekallikrein, AT III and platelet count was reduced during the first week after admission[14].

RDW, an indice of variability of erythrocyte size, has been reported as a predictor of mortality in some conditions such as cardiac disease, strokes, infections and peripheral artery disease[17]. Hu *et al*[17] evaluated the RDW in various liver diseases. RDW was found to be increased in the patients and was positively correlated with bilirubin, creatinine levels, protrombin time, and negatively correlated with platelet count and albumin level. It was stated that as the half life of red blood cells is higher than bilirubin and albumin, RDW could be used as a more stable indice than them. Proinflammatory cytokines of sepsis have been shown to affect the survival of erythrocytes in circulation, damage the membranes and suppress the maturation and lead the larger and newer reticulocytes to enter circulation and increase RDW. Also high oxidative stress can also reduce erythrocyte survival and increase the release of large premature ones in the circulation. Sadaka *et al*[18] demonstrated that RDW on the first day of septic shock was very strongly associated with mortality and morbidity.

 As mentioned above, RDW was found to be increased in some pathologic conditions, and it was shown in acute pancreatitis as well. Some of the inflammatory cytokines that play a role in the etiology of pancreatitis affect the hemostasis and lead to coagulation abnormalities. In a recent study Chen *et al*[8] evaluated RPR to predict hepatic fibrosis stages in patients with chronic hepatitis B. By using these two indices, they stated that with such a simple and non-invasive method, liver biopsy necessity will be reduced because they found that this ratio provided the greatest value of liver fibrosis. In a study from our clinic, Şenol *et al*[19] demonstrated that increased RDW level was found to be an independent predictor of mortality in AP patients. Based on this study, we researched whether RPR could be useful for assessing the mortality of patients with AP. Then we evaluated these parameters for our patients on hospital admission.

 Early recognition of the disease severity and early treatment interventions are very important and reduce the rates of morbidity and mortality. Severe AP needs urgent management, admission to an intensive care unit, optimization of oxygen delivery and maintenance of tissue perfusion. İmproved outcome is associated with early restoration of blood volume circulation[20]. So careful monitoring of patients with AP improves survival. Consistent with the correlations mentioned above we found that RPR may predict mortality in patients with AP. CBC is a simple and inexpensive laboratory test that we routinely use in clinical practice and these two indices will help us to recognize the mortality rate of the disease.

 In our study we found that if RPR is used in clinical practice with the accompanying assessments, this could be useful as an important marker for predicting the mortality of patients with acute pancreatitis.

**COMMENTS**

***Background***

Acute pancreatitis, one of the most frequent gastrointestinal causes of hospital admission, requires early diagnosis and management in order to maximize organ support and to prevent irreversible organ dysfunction. For evaluating the severity of the disease, several scoring systems and simple predictors can be used.

***Research frontiers***

Red cell distribution width (RDW) and platelet count are the two parameters in a complete blood count, and by using these indices RDW to platelet ratio can be calculated easily. In a recent study, as this ratio have shown to reflect the severity of inflammation in patients with chronic hepatitis B, authors aimed to evaluate the severity of patients with acute pancreatitis with RDW to platelet ratio (RPR) on hospital admission.

***Innovations and breakthroughs***

There are several clinical, laboratory, radiologic factors and scoring systems that have been used for evaluating the severity of acute pancreatitis. But sometimes it is not clinically practice to use these scoring systems for evaluation. So an easy and useful method is needed for predicting the severity. Therefore they wondered if RPR could be a useful marker for this purpose.

***Applications***

Authors found that RPR may predict the mortality in patients with acute pancreatitis, so if it is used in clinical practice with the accompanying assessments, this could be useful as an important marker for predicting the mortality of patients with acute pancreatitis.

***Terminology***

RPR, an easily calculated index can predict the mortality of patients with acute pancreatitis.

***Peer review***

The authors examined the accuracy of RPR for prediction of in-hospital mortality in acute pancreatitis. The performance of RPR was compared with Ranson criteria for predicting the mortality rate and found to be more sensitive than this severity score.

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**Figure 1 Receiver operating characteristic curve analysis of red cell distribution width to platelet ratio levels**. ROC: Receiver operating characteristic.



**Table 1 Summary of the demographic and clinical characteristics of the patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Nonsurvivors (*n* = 13)** | **Survivors** **(*n* = 89)** | **Univariate *P*** | **Multivariate *P*** |
| Age | 52(41-72) | 77(73-82) | 0.001 | NS |
| Sex (M/F) | 4/9 | 39/50 | NS |  |
| BUN (mg/dL) | 20.56 (12.29-48.6) | 12.66 (10.28-17.76) | 0.001 | NS |
| RDW1 | 15.6% (14%-21%) | 13.3% (12.5%-14.3%) | 0.000 | 0.001 |
| RDW/PLT ratio1 | 0.000080347 | 0.000058203 | 0.000 | 0.001 |
| Hematocrit | 45.5 (37.2-49.5) | 41.7 (37.9-45.2) | NS |  |
| Platelet count (thousand per μL) | 193 (173-212) | 236 (197-298) | 0.037 | NS |
| Amylase (U/L) | 1223 (820-2860) | 1114 (614-1663) | NS |  |
| WBC count (thousand per μL) | 14.4 (12.9-16.) | 11.4 (8.2-14.3) | 0.018 | NS |
| Albumin (g/L) | 29 (22-31) | 35 (30-38) | 0.001 | NS |
| Total bilirubin (mg/dL) | 2 (1.5-2.7) | 2 (0.90-3.60) | NS |  |
| Lactate dehydrogenase (U/L) | 274 (185-331) | 301 (195-481) | NS |  |
| Alanine aminotransferase (U/L) | 77 (29-108) | 118 (30-291) | NS |  |
| Aspartate aminotransferase (U/L) | 121 (38-186) | 122 (41-253) | NS |  |
| Calcium (mg/dL) | 7.84 (7.39-8.49) | 8.75 (8.32-9.13) | 0.001 | NS |
| Serum glucose (mg/dL) | 149 (128-200) | 138 (112-172) | NS |  |
| Hospital stay | 3 (2-19) | 6 (3-9) | NS |  |

1Bold indicates statistical significance. Data are presented as median value (interquartile range). BUN: Blood urea nitrogen; WBC: White blood cell; RDW: Red cell distribution width; PLT: Platelet count; NS: Non-significant.