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Prognostic value of red blood cell distribution width for severity in acute biliary pancreatitis

Valor pronóstico del ancho de distribución eritrocitaria para severidad en pancreatitis aguda biliar

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Palabras clave:
pancreatitis aguda, biometría hemática, índices eritrocitarios, ancho de distribución eritrocitaria.

ABSTRACT

Introduction: acute biliary pancreatitis is the most common disease of the exocrine pancreas worldwide. Its morbidity and mortality are directly related to the severity of the disease, so one of the main goals at hospital admission is to identify those patients at higher risk of developing complications. The red cell distribution width (RDW) measures the cell blood count, showing prognostic value in septic or critically ill patients. **Objective:** to determine whether levels of RDW on admission were associated with the prognosis of severity in acute biliary pancreatitis. **Material and methods:** in a nested case-control study in a cohort of patients with acute biliary pancreatitis, a total of 106 patients, grouped according to the classification of Atlanta 2012, were studied. **Results:** RDW values at admission were compared between groups, and a statistically significant difference was found between them. ROC curve analysis was performed, with an area under the curve of 0.834, 95% CI 0.707-0.961; with an RDW cut-off value of 14.95%, an Odds Ratio of 10.421 (p = 0.001) was obtained, with a sensitivity and specificity of 73.3 and 79.1% for developing severe pancreatitis. **Conclusions:** we found an association between RDW value on admission and severity of acute biliary pancreatitis. Patients with RDW >14.95% on admission are at increased risk of developing severe pancreatitis, so knowing this value will allow early identification of patients with an increased risk of developing systemic complications.

RESUMEN

Introducción: *la pancreatitis aguda es la patología más frecuente del páncreas exocrino en el mundo. Su morbimortalidad está directamente relacionada con la severidad del cuadro, por lo que uno de los principales objetivos al ingreso hospitalario es identificar aquellos pacientes con mayor riesgo de desarrollar complicaciones. El ancho de distribución eritrocitaria (ADE) es un índice de la biometría hemática que ha demostrado tener valor pronóstico en pacientes sépticos o críticamente enfermos.* ***Objetivo:*** *determinar si los niveles del ADE al ingreso se asocian con el pronóstico de severidad en pancreatitis aguda biliar.* ***Material y métodos:*** *estudio de casos y controles anidado en una cohorte de pacientes con diagnóstico de pancreatitis aguda biliar. Se estudiaron 106 casos, agrupados de acuerdo con la clasificación de Atlanta 2012.* ***Resultados:*** *se compararon los valores del ADE al ingreso entre los grupos, encontrando una diferencia estadísticamente significativa entre ellos. Se realizó análisis mediante curva ROC (área bajo la curva de 0.834, IC95% 0.707-0.961) y con un valor de ADE de 14.95%, se obtuvo una razón de momios de 10.421 (p = 0.001) para desarrollar pancreatitis grave (sensibilidad de 73.3%, especificidad de 79.1%).* ***Conclusiones:*** *encontramos asociación entre el valor del ADE al ingreso y la severidad de la pancreatitis aguda biliar. Los pacientes con un ADE > 14.95% al ingreso tienen mayor riesgo de cursar con un cuadro de pancreatitis grave, por lo que conocer este valor al ingreso permitirá identificar tempranamente aquéllos con mayor riesgo de desarrollar complicaciones sistémicas.*

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INTRODUCTION

Acute pancreatitis is the most frequent disease of the exocrine pancreas worldwide; it comprises a broad clinical spectrum ranging from self-limited pancreatic involvement, with resolution of the inflammatory picture and complete recovery in a few days, to systemic involvement that can trigger sepsis, multiple organ failure and patient's death.[1] The most frequent etiology in our environment is biliary.[2-4]

It is considered that 80% of the cases will have mild disease (mortality < 1%), while the remaining 20% will present severe disease with mortality up to 50%; that is, 90% of the deaths occur in patients with severe acute pancreatitis.[5,6]

The most widely used classification at present is the Atlanta classification; the latest revision of this classification in 2012 aims to unify the diagnostic criteria in acute pancreatitis, define local and systemic complications, and propose a new classification according to the pathophysiology and evolution of the cases, recognizing three degrees of severity: In this context, severe acute pancreatitis is defined as that which presents with persistent organ failure (greater than 48 hours); this organ failure develops during the early phase of pancreatitis, triggering a systemic inflammatory response that perpetuates the organ failure, which may be single or multiple, and may or may not be accompanied by local complications. In these patients, mortality is reported to be as high as 36-50%.[6]

Early determination of the severity of pancreatitis is crucial to recognize those at higher risk of complications and those requiring intensive monitoring and treatment.[1,7,8] To this end, several clinical and biochemical scales have been described; however, most require multiple laboratory determinations and the performance of several laboratory studies; most are expensive and unavailable in all hospital units.[6,8-15]

The erythrocyte distribution width (EDW) is a parameter of cell blood count that describes the percentage of heterogeneity in the size of erythrocytes and is part of the complete test.[16,17] It is calculated by dividing the standard deviation (SD) by the mean of the mean corpuscular volume (MCV) and multiplying this value by 100 (ADE = [SD/VCM] × 100). It is routinely included in automated blood counts and is therefore available in clinical practice at no additional cost. The physiological ADE value in our population is 12.8 ± 0.7 in women and 12.6 ± 0.7 in men. The higher the value, the greater the heterogeneity. An RDW of more than 15% implies an abnormally heterogeneous cell population, i.e., anisocytosis.[18]

In addition to being a useful parameter in the study of anemias, in recent years, various studies have shown its prognostic value in subjects with heart failure, acute myocardial infarction, pulmonary thromboembolism, pneumonia, critically ill patients and cardiac arrest, as well as in other chronic diseases.[19-28]

The mechanisms involved in this association need to be better clarified. It has been described that the systemic inflammatory response, the presence of inflammatory cytokines, and nutritional deficits lead to increased ADE values. Similarly, an association between ADE-bacteremia and ADE-sepsis has been reported, so it has been used as a biomarker of underlying conditions, inflammatory processes, oxidative damage, and malnutrition.

In 2013, Kolber[29] published the first study to describe an association between increased RDW and mortality in acute pancreatitis. Subsequently, Senol[30] also described the usefulness of ADE as an independent prognostic marker of mortality in cases with acute pancreatitis. These observations were also reported by Yao[31] and Zhang,[32] who described higher levels of RDW in non-survivors concerning survivors with acute pancreatitis and healthy controls.

Objective: to determine whether RDW levels at hospital admission correlate with prognostic severity in acute biliary pancreatitis.

MATERIAL AND METHODS

A prospective nested case-control study in a cohort of patients admitted to the general surgery service diagnosed with acute pancreatitis of biliary etiology from May 2013 to January 2014, which were grouped according to the Atlanta 2012 classification, was performed.

With the difference of proportions formula, a sample size of 110 cases was calculated. Demographic variables, laboratory values, ADE at admission, with follow-up of the evolution to three months, local and systemic complications and their duration, days of hospital stay, and deaths, if any, were recorded.

Adults of both genders with a diagnosis of acute pancreatitis of biliary origin were included. Pregnant patients, oncologic patients, patients from other units with complications of acute pancreatitis but without acute symptoms, patients with a history of blood transfusion in the last 120 days, or patients diagnosed with anemia or other hematologic diseases were excluded. Patients with incomplete records or those in whom it was impossible to complete the follow-up were eliminated.

Ethical aspects: the Ethics and Research Committees of the Hospital General de México reviewed the protocol approved by the Directorate of Research, with registration code DI/13/305/03/042. Informed consent was obtained in all cases, and the information was handled confidentially.

Table 1: Erythrocyte distribution width values by group according to the Atlanta 2012 classification.

	Erythrocyte distribution width	
Atlanta	**n (%)**	**mean ± SD**
Mild	54 (50.9)	14.04 ± 1.11
Moderately severe	37 (34.9)	14.51 ± 0.98
Severe	15 (14.2)	15.99 ± 1.51

Table 2: Comparison of erythrocyte distribution width according to the presence of local complications.

	Erythrocyte distribution width	
	n (%)	**mean ± SD**
Absent	87 (82.07)	14.38 ± 1.23
Present	19 (17.92)	14.92 ± 1.52

Statistical analysis: we analyzed descriptive and inferential statistics, finding normal distribution in our variable. A general linear model, ANOVA with Bonferroni post hoc test, considering a statistically significant a value of $p < 0.05$, ROC curve, diagnostic validation tests and contingency tables with calculation of odds ratio. SPSS® version 22 was used for the statistical analysis.

RESULTS

A total of 106 cases with acute pancreatitis of biliary origin were included. The study sample consisted of 80 women (75.5%) and 26 men (24.5%), with a mean age of 41.41 years (range 18 to 88) with an SD ± 19.38. The most frequent comorbidities were: overweight and obesity (37.7% and 26.4%), followed by systemic arterial hypertension (16%) and diabetes mellitus (4.7%).

They were grouped according to the 2012 Atlanta classification criteria *(Table 1)*. ADE values at admission were compared between groups through the ANOVA test, finding a significant difference ($p < 0.001$). The Bonferroni test showed that patients with severe acute pancreatitis had significantly higher RDW values ($p < 0.001$) than those with mild and moderately severe acute pancreatitis.

Nineteen subjects recorded the presence of local complications. When comparing the ADE between cases without local complications and those with local complications, no significant difference was found between the two groups ($p = 0.105$) *(Table 2)*.

Regarding systemic complications, a distinction was made between subjects where the systemic complication resolved in less than 48 hours (transient failure) and those where it persisted for more than 48 hours (persistent failure). Within the group with transient complications, 34 cases (32.1%) were found; renal and metabolic failure (metabolic acidosis and hyperglycemia) were the most frequent, followed by pulmonary and decompensation of previous heart disease. When comparing the ADE between patients without complications and those with transient systemic complications, no significant

Table 3: Comparison of erythrocyte distribution width according to systemic complications.

	Erythrocyte distribution width	
	n (%)	mean ± SD
Absent	54 (50.9)	14.04 ± 1.09
< 48 hours	34 (34.9)	14.55 ± 0.99
< 48 hours	15 (14.2)	15.99 ± 1.51

difference was found between the values in both groups (14.04 vs. 14.55%; p = 0.116).

Within the group with persistent systemic complications, 15 patients were found; renal failure was the most frequent complication, followed by pulmonary, hematologic, metabolic, and sepsis conditions. When comparing the RDW between patients without complications and those with persistent systemic complications, a statistically significant difference was found between the values in both groups (14.04 vs. 15.99%, p < 0.001).

When comparing the ADE between those with transient systemic complications and those with persistent systemic complications, the difference between the values in both groups was also statistically significant with p < 0.001 *(Table 3)*.

By means of a general linear univariate model, it was observed that there was a higher RDW value at admission in subjects with severe pancreatitis (p < 0.001).

A ROC curve was performed to determine the RDW value at patient admission, with greater diagnostic utility to detect cases with severe acute pancreatitis, obtaining an area under the curve of 0.834, a standard error of 0.065 and a p < 0.001, with a 95% confidence interval of 0.707-0.961. When analyzing the coordinates of the curve, we observed that with an ADE value at admission of 14.95% or higher, we obtained a sensitivity of 73.3% and a specificity of 79.1% to predict severe acute pancreatitis and an odds ratio of 10.421 (significant with a χ^2 value 17.461 and p < 0.001) *(Table 4 and Figure 1)*.

ADE levels were analyzed at admission, 48, 72, and 168 hours in patients with these measurements (n = 82). A high correlation (R = 0.88 at 48, R = 0.801 at 72, and R = 0.728 at 168 hours) was found between values at admission and on days two, three, and seven of hospital stay.

DISCUSSION

Within the treatment of cases with acute pancreatitis, it is of vital importance to determine when an acute pancreatitis event is going to become severe; this allows the identification

Table 4: Diagnostic test value.

Variable	Percent
Erythrocyte distribution width	> 14.95
Sensitivity	73.33
Specificity	79.12
PPV	36
NPV	94
Overall Value	78

PPV = positive predictive value.
NPV = negative predictive value.

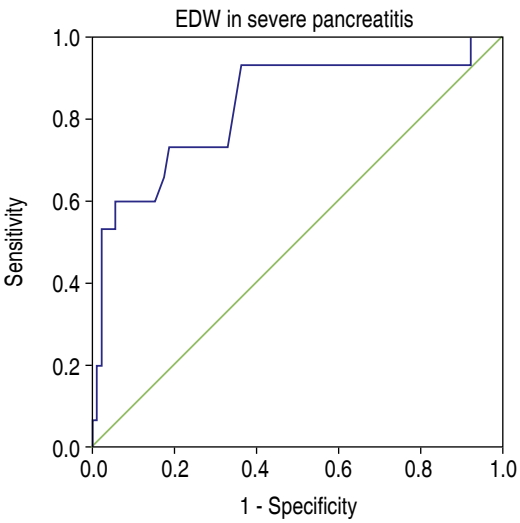

Figure 1: *Receiver Operating Characteristic (ROC) curve for erythrocyte distribution width in severe pancreatitis. Ties generate diagonal segments.*
EDW = erythrocyte distribution width.

of the most vulnerable patients, who require a more aggressive therapeutic approach, referral to a third level or admission to an intensive care unit, to maximize life support and prevent irreversible organ dysfunction. Risk factors for developing severe pancreatitis have been described to date, such as advanced age, associated comorbidities, and obesity. Much of the research in acute pancreatitis is directed to the search for a biomarker that allows early identification of those who will evolve to severe forms, such as C-reactive protein, D-dimer, determination of metalloproteinases, or serum amyloid A.

This study established the usefulness of RDW as a predictor of severity in acute pancreatitis of biliary origin, explored the prognostic correlation between RDW and the severity of biliary pancreatitis, and proposed a cut-off point for screening and early identification of patients at risk. Unlike other scales or risk markers currently used in acute pancreatitis, RDW is routinely performed as part of the blood cell count measure. Hence, its determination upon patient admission to an emergency department is fast, automated, and inexpensive, and its availability is practically universal.

RDW was determined in all patients on admission to the emergency department, even before confirming the diagnosis of acute pancreatitis. When comparing the RDW values of patients with severe acute pancreatitis versus those who developed mild or moderately severe forms, we found an association between the admission levels and the severity of pancreatitis. There is a tendency to have higher levels in patients who developed persistent systemic complications; when analyzing the mean difference between the three groups, we found that this was statistically significant in the severe pancreatitis group concerning the other two groups (14.04 vs. 14.51 vs. 15.99%).

We sought to establish an ADE value at admission that would predict severe acute pancreatitis, defined according to the 2012 revision of the Atlanta classification as the presence of persistent organ failure, regardless of the presence of local complications. Using the ROC curve, it was found that with a cut-off point of 14.95%, the ADE has a sensitivity of 73.3% and a specificity of 79.1% to predict severe pancreatitis. With this cut-off point, it was observed that patients with an ADE value at admission > 14.95% have a 10-fold increased risk of developing severe acute pancreatitis compared to cases with a lower ADE at admission.

Even though there are no studies on the usefulness of RDW as a predictor of severity, these results are consistent with previous studies by Senol,[30] Yao[31] and Kolber,[29] who established its usefulness as a predictor of mortality in pancreatitis. In our study, only two deaths were recorded, corresponding to an overall mortality rate of 1.88%, like that reported in the literature. Both cases were in the severe pancreatitis group, which gives us mortality for this group of 13.3%, like that reported in the international literature. Since the number of deaths was low in this study, it was impossible to establish whether the ADE had prognostic value for predicting mortality in our population, as suggested by other authors.

We did not observe differences in RDW levels at admission about local complications. Even when these complications are caused by extensive local tissue destruction, they do not impact mortality. This supports the theory that RDW is a biomarker of pre-existing systemic inflammatory conditions rather than the acute inflammatory response caused by pancreatitis. Thus, elevated RDW will be associated with systemic conditions that favor the development of severe pancreatitis independently of local inflammatory damage.

When analyzing the levels of RDW at admission, 48, 72, and 168 hours, a high correlation was found, suggesting that its determination in the first seven days of pancreatitis' evolution will present few variations; this low variability supports the theory that the modifications are due to underlying chronic clinical conditions.

CONCLUSIONS

An elevated RDW on admission to the emergency department allows us to identify vulnerable cases with a higher risk of developing severe acute pancreatitis of biliary origin.

Although we do not know the pathophysiology of anisocytosis in these

patients, these observations indicate that it is possible to use RDW as an early marker of severity in patients with acute pancreatitis of biliary origin; these results are compatible with observations made in other parts of the world. We know that early identification of severe cases of acute biliary pancreatitis allows modifying the evolution, seeking to improve the prognosis; in this sense, ADE can become a tool available to any hospital unit for initial screening, thus optimizing its treatment.

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