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Original article

Red Cell Distribution Width and Additive Risk Prediction for Major Bleeding in Non–ST-segment Elevation Acute Coronary Syndrome

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ABSTRACT

Introduction and objectives: Red cell distribution width has been linked to an increased risk for in-hospital bleeding in patients with non–ST-segment elevation acute coronary syndrome. However, its usefulness for predicting bleeding complications beyond the hospitalization period remains unknown. Our aim was to evaluate the complementary value of red cell distribution width and the CRUSADE scale to predict long-term bleeding risk in these patients.
Methods: Red cell distribution width was measured at admission in 293 patients with non–ST-segment elevation acute coronary syndrome. All patients were clinically followed up and major bleeding events were recorded (defined according to Bleeding Academic Research Consortium Definition criteria).
Results: During a follow-up of 782 days [interquartile range, 510-1112 days], events occurred in 30 (10.2%) patients. Quartile analyses showed an abrupt increase in major bleedings at the fourth red cell distribution width quartile ($>$ 14.9%; $P = .001$). After multivariate adjustment, red cell distribution width $>$ 14.9% was associated with higher risk of events (hazard ratio = 2.67; 95% confidence interval, 1.17-6.10; $P = .02$). Patients with values $\leq$ 14.9% and a CRUSADE score $\leq$ 40 had the lowest events rate, while patients with values $>$ 14.9% and a CRUSADE score $>$ 40 points (high and very high risk) had the highest rate of bleeding (log rank test, $P < .001$). Further, the addition of red cell distribution width to the CRUSADE score for the prediction of major bleeding had a significant integrated discrimination improvement of 5.2% ($P < .001$) and a net reclassification improvement of 10% ($P = .001$).
Conclusions: In non–ST-segment elevation acute coronary syndrome patients, elevated red cell distribution width is predictive of increased major bleeding risk and provides additional information to the CRUSADE scale.

Ancho de distribución eritrocitaria y predicción adicional del riesgo de hemorragia mayor en el síndrome coronario agudo sin elevación del ST

Palabras clave:
Ancho de distribución eritrocitaria
Hemorragia
Síndrome coronario agudo

RESUMEN

Introducción y objetivos: El ancho de distribución eritrocitaria se ha relacionado con incremento del riesgo hemorrágico intrahospitalario en pacientes con síndrome coronario agudo sin elevación del ST. Sin embargo, se desconoce su utilidad para predecir complicaciones hemorrágicas tras el ingreso hospitalario. El objetivo fue evaluar el papel complementario del ancho de distribución eritrocitaria sobre la escala CRUSADE en la predicción del riesgo a largo plazo de hemorragias en estos pacientes.
Métodos: Se midió el ancho de distribución eritrocitaria al ingreso en 293 pacientes con síndrome coronario agudo sin elevación del ST; a todos se les dio seguimiento clínico y se registró la aparición de hemorragias mayores, definidas según los criterios del *Bleeding Academic Research Consortium*.
Resultados: Durante un seguimiento de 782 [intervalo intercuartílico, 510-1.112] días, 30 pacientes (10,2%) presentaron eventos hemorrágicos. El análisis por cuartiles reveló un incremento abrupto de hemorragias a partir del cuarto cuartil ($>$ 14,9%; p = 0,001). Tras el análisis multivariable, el ancho de distribución eritrocitaria $>$ 14,9% se asoció con mayor riesgo de eventos (*hazard ratio* = 2,67; intervalo

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de confianza del 95%, 1,17-6,10; p = 0,02). Los pacientes con valores ≤ 14,9% y CRUSADE ≤ 40 presentaron las menores tasas de hemorragias, mientras que los pacientes con valores > 14,9% y CRUSADE > 40 puntos (alto y muy alto riesgo) presentaron las mayores (log rank test, p < 0,001). Además, la adición del ancho de distribución eritrocitaria a la escala CRUSADE para predecir hemorragias mostró tasas de mejora integrada del 5,2% (p < 0,001) y de reclasificación del 10% (p = 0,001).

Conclusiones: Los valores elevados del ancho de distribución eritrocitaria se asocian a mayor riesgo hemorrágico y aportan información adicional a la escala CRUSADE.

Abbreviations

ACS: acute coronary syndrome
MB: major bleeding
NSTEACS: non–ST-segment elevation acute coronary syndrome
RDW: red cell distribution width

INTRODUCTION

Hemorrhagic complications represent an important adverse prognostic factor in patients with acute coronary syndromes (ACS).[1–3] Previous studies indicate that patients with major bleeding (MB) in this setting have up to a 20% of risk of death, myocardial infarction, or stroke during the first 30 days compared with 5% in those who do not develop MB during the first 30 days.[1] This risk extends beyond the time of procedures, and even when the severity of the bleeding does not indicate that it is life-threatening.[1] Mechanistically, the risk associated with MB is thought to be multifactorial, resulting from the interruption of effective antithrombotic drugs, the reduction of oxygen delivery to the myocardium as a result of hypoperfusion, platelet activation, and the potentially adverse effects of transfusion.[4]

Given the deleterious association between MB and outcome in ACS, the identification of risk factors able to predict hemorrhage is important and has been explored using clinical risk models. It is logical to explore laboratory factors as well as to provide information to complement bleeding risk scales. Red cell distribution width (RDW) is a quantitative measure of the variability in size of the circulating erythrocytes,[5] and has been recently found to be strongly predictive of cardiovascular outcomes in multiple patient populations, including those with ACS.[6–12]

Most recently, increased RDW has also been linked to a higher rate of bleeding in patients with ACS.[13,14] However, these studies assessed only the role of RDW for the prediction of in-hospital bleeding, and did not report the usefulness of RDW for the prediction of bleeding during follow-up.

Therefore, the objective of the present study was to assess the role of RDW values to predict risk of MB over the long-term follow up of patients with non–ST-segment elevation ACS (NSTEACS), and to evaluate whether RDW adds additional predictive value to a widely accepted model for predicting MB risk, the CRUSADE scale.[15]

METHODS

Subjects and Study Design

From September 2006 to December 2008, we prospectively enrolled 293 consecutive patients with an established final diagnosis of high-risk unstable angina or non–ST-segment elevation myocardial infarction. High-risk NSTEACS was defined as ischemic symptoms lasting ≥ 10 min and occurring within 72 h before admission and either ST-segment deviation ≥ 1 mm or elevated levels of cardiac biomarker of necrosis.[16] Patients with evidence of infectious, connective tissue or inflammatory disease were excluded, as were patients taking iron supplements, folic acid, vitamin B_{12} or immunosuppressant agents. Furthermore, patients who refused or were incapable of giving informed consent were also excluded.

During the entire hospitalization period, baseline clinical characteristics were prospectively recorded. Risk of MB was calculated using CRUSADE risk scale. Patients were classified into 5 categories as a function of the CRUSADE risk scale: very low, ≤ 20 points; low, 21 points to 30; moderate, 31 to 40 points; high, 41 points to 50 points; and very high risk, > 50 points. The clinical management decisions about each patient were taken by the responsible cardiologist, who had clinical access to the RDW value. The study was approved by the local ethics committee, and informed consent was obtained from each patient at inclusion.

Biochemistry

All blood samples were obtained on arrival at the emergency department and were processed immediately after extraction. All hematological parameters were determined using the XE-2100 automatic analyzer (Sysmex; Kobe, Japan) and all biochemical parameters using the PE modular analyzer (Roche Diagnostics; Manheim, Germany). Anemia was defined according to the World Health Organization criteria[17]: hemoglobin < 13 g/dL for men and < 12 g/dL for women. Renal function data were estimated from the calculation of the estimated glomerular filtration rate (mL/min/1.73 m^2) using the Cockroft-Gault[18] (estimated glomerular filtration rate formula: ([140 − age] × weight [kg]) / (serum creatinine [mg/dL] × 72) (× 0.85 for women).

Follow-up and Endpoints

After hospital discharge, patients were followed up for a median of 782 days [interquartile range, 510-1112 days]. All medical records were carefully reviewed, and the patients or their relatives were contacted by telephone to obtain the incidence of bleeding events during the follow-up. The clinical endpoint was defined as the occurrence of MB, which was defined according to the Bleeding Academic Research Consortium Definition criteria[19] as bleeding types 3 to 5; type 3 a, overt bleeding plus hemoglobin drop of of 3 g/dL to 5 g/dL, any transfusion with overt bleeding; type 3 b, overt bleeding plus hemoglobin drop 5 g/dL, cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), bleeding requiring iv vasoactive agents; type 3 c, intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision; type 4, coronary