

Performance of a Hematological Scoring System in Predicting All-Cause Mortality in Patients with Acute Myocardial Infarction

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Abstract

Background: The presence of nucleated red blood cells (NRBCs) and increases in mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR) in peripheral circulation are associated with poorer prognosis in patients with acute coronary disease.

Objective: We developed a scoring system for in-hospital surveillance of all-cause mortality using hematological laboratory parameters in patients with acute myocardial infarction (AMI).

Methods: Patients admitted for AMI were recruited in this prospective study. Exclusion criteria were age younger than 18 years, glucocorticoid therapy, cancer or hematological diseases and readmissions. NRBCs, MPV and NLR were measured during hospitalization. The scoring system was developed in three steps: first, the magnitude of the association of clinical and laboratory parameters with in-hospital mortality was measured by odds ratio (OR), second, a multivariate logistic regression model was conducted with all variables significantly ($p < 0.05$) associated with the outcome, and third, a β -coefficient was estimated by multivariate logistic regression with hematological parameters with a $p < 0.05$.

Results: A total of 466 patients (mean age were 64.2 ± 12.8 years, 61.6% male) were included in this study. A hematological scoring system ranging from 0 to 49, where higher values were associated with higher risk of in-hospital death. The best performance was registered for a cut-off value of 26 with sensitivity of 89.1% and specificity of 67.2%, positive predictive value of 26.8% (95% CI: 0.204 – 0.332) and negative predictive value of 97.9% (95% CI: 0.962 – 0.996). The area under the curve for the scoring system was 0.868 (95% CI: 0.818 – 0.918).

Conclusions: Here we propose a hematological scoring system for surveillance tool during hospitalization of patients with acute myocardial infarction. Based on total blood count parameters, the instrument can evaluate inflammation and hypoxemia due to in-hospital complications and, consequently, predict in-hospital mortality. (Int J Cardiovasc Sci. 2020; 33(4):380-388)

Keywords: Myocardial Infarction; Coronary Artery Diseases; Severity of Illness Index; Mortality; Scoring System; Nucleated Red Blood Cells; Mean Platelet Volume; Neutrophil to Lymphocyte Ratio.

Introduction

Acute myocardial infarction (AMI) is the main cause of death in the world and the prevalence is rising in developing countries.¹ According to previous studies, the

mortality has been declining in higher-income countries, and it has generally been attributed to greater use of preventive measures, adherence to current guidelines and revascularization procedures.^{1,2} A recent paper, published by our research group, showed that the

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presence of nucleated red blood cells (NRBCs), and increases in the neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) in peripheral blood of patients hospitalized with AMI are associated with a poorer prognosis.³

The bone marrow is responsible for producing blood cells (red blood cells, leucocytes and platelets), by a process called hematopoiesis, which originates from a single progenitor cell called the stem cell. Pluripotent stem cells, existing in small amounts in the bone marrow, can reproduce when necessary and lead to differentiation processes in different hematological cell lines.⁴ Growth inducers promote multiplication but not differentiation of the stem cells. This is the function of another group of proteins, called differentiation inducers, which are controlled by factors external to the bone marrow. For example, in case of red blood cells, exposure to low oxygen concentrations over a long period results in the induction of growth, differentiation and increased production of red blood cells. This stimulus to the bone marrow is produced by erythropoietin, a glycoprotein primarily (90%) produced in the kidneys, but also in the liver, in response to hypoxemia. Prior studies have shown that severe hypoxemia and infection are the main cause of synthesis of NRBCs, and increases in NLR and MPV in peripheral blood, when hematological diseases, cancer, congestive heart failure, acute and chronic anemias are excluded.⁵⁻¹³

The aim of this study was to propose a scoring system for these hematological variables. Actual and reproductive variability of these hematological biomarkers during hospitalization of these patients could be a predictor of all-cause mortality and help the medical team in diagnostic and therapeutic decision.

Materials and methods

Ethics Statement

This study is part of the project (Neutrophil to Lymphocyte Ratio, Mean Platelet Volume and Erythroblast as prognostic biomarkers in patients with AMI) approved by the Ethics Committee of the Hospital Complex HUOC/PROCAPE of the University of Pernambuco under number CAAE: 51802115.7.0000.5192 (Brazil Platform). The research was conducted according to the principles of the Declaration of Helsinki.

Study Design

The present study proposes a scoring system based on β -coefficient values estimated by multivariate logistic regression model adjusted for NRBC, MPV and NLR in patients hospitalized with AMI. In logistic model, these coefficients are obtained using the method of maximum likelihood and they represent the probabilistic change in one variable when all others are fixed. The coefficient β of each variable was multiplied by 10 to optimize the rounding. Subsequently, accuracy parameters were calculated.

All patients included in the study were followed up by researchers from hospital admission to discharge. Management of these patients was established based on well-defined protocols for primary angioplasty, myocardial revascularization surgery or clinical treatment. Data on clinical course and laboratory tests of the patients were obtained daily from electronic medical records by the authors of the study.

Study Population

All consecutive patients admitted with AMI to PROCAPE, a tertiary teaching hospital with 250 beds, referral for emergency cardiac care, between January 1, 2016 and September 30, 2016 were included. We excluded patients younger than 18 years, on glucocorticoid therapy, patients with cancer or hematological diseases, and those readmitted after hospital discharge. All patients signed an informed consent form to participate in the study.

Definition of terms and study variables

The diagnosis of AMI was established based on clinical, electrocardiographic and laboratory (troponin) criteria.^{2,3} As for electrocardiography, myocardial infarction can be divided into ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (non-STEMI).^{2,3} With respect to the KILLIP and TIMI Risk scores, patients were classified into low risk (KILLIP I to II and TIMI Risk 0 to 3) and high risk (KILLIP III to IV and TIMI Risk 4 to 7). Potential risk factors associated with AMI such as demographic characteristics (age, gender), systemic arterial hypertension (blood pressure $\geq 140 \times 90$ mmHg), diabetes mellitus (plasma glucose above 126 mg/dL), smoking habit (yes or no), sedentary lifestyle (regular practice of physical exercise or not), kidney disease (creatinine above 1.3 mg/dL) and

depression (use of medicine or not) were adjusted for the statistical model.³

For patients' stratification according to the Killip classification, the following categories were used: I – normal, II – heart failure, III - acute lung edema, IV – cardiogenic shock.¹⁴ The TIMI Risk score to non-STEMI is based on 7 variables – age ≥ 65 years, ≥ 3 risk factors for coronary artery disease, previous cardiac catheterization (stenosis $> 50\%$), electrocardiography (ST-segment depression ≥ 0.5 mm), anginal symptoms, use of acetylsalicylic acid (ASA) in the last 7 days, and elevated troponin levels.¹⁵

Complete blood count parameters including NRBCs, leukocytes, neutrophils, lymphocyte, platelet, MPV were measured using a Sysmex XE-2100 blood analyzer (Sysmex, Kobe, Japan). A positive NRBC was defined as any value above zero; cut-off level for high MPV was ≥ 10.4 fL, and NRL was calculate by dividing the neutrophil count by the lymphocyte count, with a high cut-off level of ≥ 3.7 , as previously described.⁵⁻⁷ Blood samples were collected between 24 and 48 hours after admission.

Statistical analysis

The scoring system was developed in three steps (Figure 1). Multiple linear and multivariate logistic analysis of hematological variables and cardiovascular risk factors were used to identify independent predictors of mortality. In the first step, the magnitude of association of clinical and laboratory parameters with in-hospital mortality were measured by odds ratio (OR), whose statistical significance was estimated by likelihood ratio (Pearson chi-squared test) and represented by p-value. In the second step, the multivariate logistic regression model was conducted with all variables with a p value < 0.05 and the outcomes remained in the model. In the third step, another adjusted logistic regression was calculated, with hematological parameters with $p < 0.05$ and a coefficient β (strength of association between variables). A score was attributed to each variable, which was the coefficient β of each variable multiplied by 10, for the sake of rounding off. To analyze the accuracy of the scoring system, a receiver operating characteristic (ROC) curve was constructed, and sensitivity, specificity, positive and negative predictive values, positive (LR+) and negative (LR-) likelihood ratios, with their respective confidence intervals, were calculated.

Continuous variables were expressed as mean \pm standard deviation (normal distribution) or median

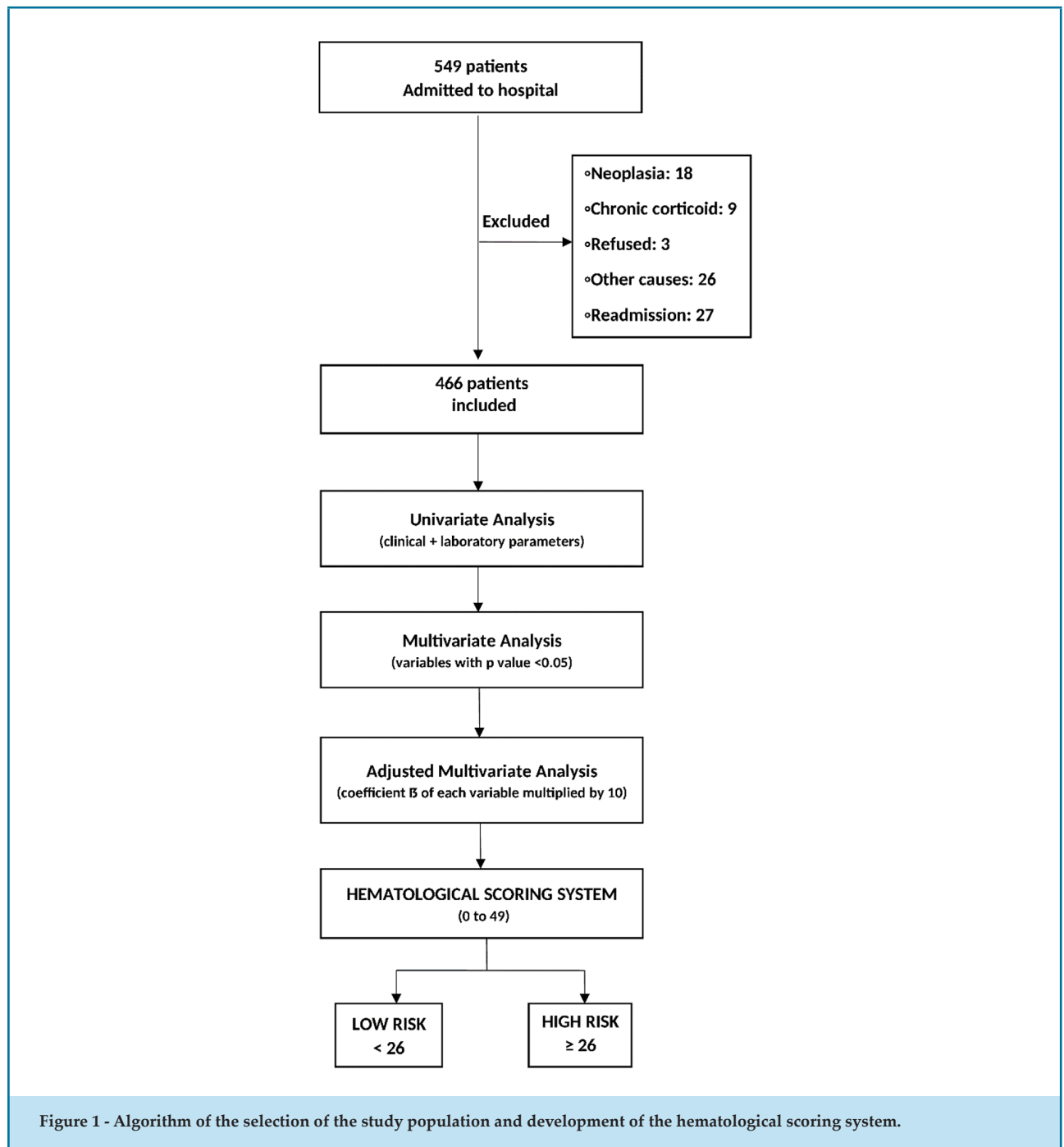
(without normal distribution) and categorical variables were expressed as absolute or percent values, as appropriate. The association of higher levels of NRBC, MPV and NLR with clinical and laboratory characteristics of the patients were assessed using Pearson Chi-squared test or Mann-Whitney U test. Regression analysis was performed for the variables identified as statistically significant in univariate analysis. The abilities of NRBC, MPV and NLR to distinguish patients with AMI from low or high risk of in-hospital death were evaluated using ROC curve analysis. The overall agreement between the hematological scoring system and Killip / TIMI Risk scores was assessed using Kappa coefficient. Statistical analyses were conducted using the Statistical Program for Social Sciences (SPSS), version 10.0 for Windows.

Results

A total of 466 patients (mean age 64.2 ± 12.8 years, 61.6% male) were included in this study. Total mortality was 11.8% (55 patients): 43/326 (13.2%) STEMI and 12/140 (8.6%) non-STEMI. Clinical characteristics related to in-hospital mortality among patients with AMI are described in Table 1.

The presence of NRBCs in the sample was detected in 9.1% (42 patients), 27 (5.8%) with levels $> 200/\mu\text{L}$. Mean MPV value was 10.9 ± 0.9 fL and the mean NLR value was 3.71 (2.38; 5.72). The association of in-hospital mortality with the presence of NRBCs and increases in MPV and NLR in peripheral blood is shown in Table 1. We used the univariate model to assess which clinical and laboratory factors were associated with in-hospital mortality among patients with AMI (Table 1).

To identify independent predictor variables associated with in-hospital mortality, we performed a multivariate analysis model (Table 2). After adjustment, the points assigned to each hematological variable of the scoring system proposed and respective coefficients β are detailed in Table 3. The hematological scoring system proposed had a scale ranging from 0 to 49, where higher values were associated with higher risk of in-hospital death. The better performance was registered for a cut-off value of 26 with sensitivity of 89.1% and specificity of 67.2%, positive predictive value of 26.8% (95% CI: 0.204 – 0.332) and negative predictive value of 97.9% (95% CI: 0.962 – 0.996) (Table 4). The area under the curve for the scoring system was 0.868 (95% CI: 0.818 – 0.918) (Figure 2). A score ≥ 26 points in the scoring system proposed showed an agreement of 82.1% with



KILLIP score III and IV (kappa coefficient = 0.141; 61.5% overall agreement) (Table 5) and a score < 26 showed an agreement of 81% with TIMI Risk score 0 to 3 (kappa coefficient = 0.162; 50.7% overall agreement) (Table 6).

Discussion

NRBCs, MPV, and NLR are independent predictors of all-cause mortality in AMI patients.³ These

hematological parameters are directly associated with severity of systemic inflammation and hypoxemia, and these two mechanisms are directly implicated in the pathophysiology of organic dysfunction. An intense inflammatory response is activated in the early step of cardiac ischemic injury. However, other conditions including sepsis and shock may occur during hospitalization. In this study, we propose a scoring system with these hematological parameters

Table 1 - Clinical and laboratory characteristics related to in-hospital mortality among patients with acute myocardial infarction by logistic regression

Factors	OR	CI (95%)	p-value
Age^a			
< 65 years	1.0	-	-
≥ 65 years	3.58	1.89 - 6.77	< 0.001
Sex^a			
Female	1.0	-	-
Male	1.01	0.57 - 1.80	0.970
Skin color^a			
White	1.0	-	-
Brown	0.80	0.43 - 1.50	0.485
Black	0.44	0.17 - 1.15	0.094
Classification of AMI			
Non-STEMI	1.0	-	-
STEMI	1.62	0.83 - 3.18	0.160
Risk factors			
Systemic arterial hypertension	1.88	0.92 - 3.84	0.085
Diabetes mellitus	1.75	0.99 - 3.08	0.053
Kidney disease	1.15	0.43 - 3.07	0.787
Family history of coronary heart disease	0.27	0.14 - 0.55	< 0.001
Dyslipidemia	0.76	0.42 - 1.39	0.375
Depression	0.14	0.02 - 1.01	0.051
Smoking	0.78	0.43 - 1.39	0.400
Sedentary lifestyle	1.47	0.83 - 2.59	0.187
Laboratory measures			
Erythrocyte ^b	0.18	0.11 - 0.32	< 0.001
Hemoglobin ^b	0.65	0.55 - 0.76	< 0.001
Leukocytes^c			
≤ 10,5	1.0	-	-
> 10.5	5.52	2.71 - 11.3	< 0.001
CRP^c			
≤ 36,7	1.0	-	-
> 36.7	7.98	3.44 - 18.5	< 0.001
IG%^c			
≤ 0.3	1.0	-	-
> 0.3	11.7	4.88 - 27.9	< 0.001

TNT^c			
≤ 1.87	1.0	-	-
> 1.87	2.23	1.23 - 4.05	0.008
RDW SD^c			
≤ 43.2	1.0	-	-
> 43.2	4.34	2.22 - 8.48	< 0.001
RDW CV^c			
≤ 13.5	1.0	-	-
≥ 13.5	4.22	2.16 - 8.23	< 0.001
NLR			
< 3.7	1.0	-	-
≥ 3.7	16.0	5.67 - 45.0	< 0.001
NRBC			
Absence (0)	1.0	-	-
Presence (≥ 1)	33.9	15.8 - 72.8	< 0.001
MPV			
< 10,4	1.0	-	-
≥ 10.4	3.32	1.46 - 7.55	0.004

^a per 100 person-day of hospitalization; ^b Decreased risk with the increase of one unit of the laboratory marker; ^c Risk for values above the median; OR: Odds Ratio; CI: confidence interval; CRP: c-reactive protein; IG: immature granulocyte; TNT: troponin T; RDW SD: red cell distribution width measured as standard deviation; RDW CV: red blood cell distribution width as coefficient of variation; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.

to be used for clinical surveillance during patients' hospitalization.

In the last five decades, due to scientific advances and the advent of automated counting of peripheral blood cells in a safe and reliable way, the complete blood cell count has become an important clinical tool to detect variations in hematopoietic response to existing injury. Thus, these variables reflect not only ischemia and its hemodynamic repercussions, but also inflammatory processes (infectious or not) during hospitalization that may contribute to increased mortality of AMI patients, thereby complementing the risk stratification scores currently used in the clinical practice.

In the present study, we demonstrated that the presence of NRBCs (OR 33.9, 95% CI: 15.8 - 72.8, $p < 0.001$), increases in MPV (OR 3.32, 95% CI: 1.46 - 7.55, $p = 0.004$) and NLR (OR 16.0, 95% CI: 5.67 - 45.0, $p < 0.001$) in peripheral blood was associated

Table 2 - Multivariate analysis of factors related to in-hospital mortality among patients with acute myocardial infarction by logistic regression

Factors	OR	CI (95%)	p-value	Adjusted OR	CI (95%)	p-value
Age						
< 65 years	1.0	-	-	1.0	-	-
≥ 65 years	3.58	1.89 - 6.77	< 0.001	2.94	1.25 - 6.96	0.014
Erythrocytes ^a	0.18	0.11 - 0.32	< 0.001	0.36	0.17 - 0.76	0.006
Leukocytes ^b						
≤ 10.5	1.0	-	-	1.0	-	-
> 10.5	5.52	2.71 - 11.3	< 0.001	3.83	1.48 - 9.91	0.006
Platelet ^b						
≤ 231	1.0	-	-	1.0	-	-
> 231	9.44	2.94 - 30.3	< 0.001	9.02	1.71 - 47.4	0.009
NLR						
< 3.7	1.0	-	-	1.0	-	-
≥ 3.7	16.0	5.67 - 45.0	< 0.001	4.28	1.30 - 14.1	0.017
NRBC						
Absence (0)	1.0	-	-	1.0	-	-
Presence(> 1)	33.9	15.8 - 72.8	< 0.001	10.1	4.06 - 24.9	< 0.001
MPV						
< 10.4	1.0	-	-	1.0	-	-
≥ 10.4	3.32	1.46 - 7.55	0.004	2.99	1.05 - 8.55	0.041

^a Decreased risk with the increase of one unit of the laboratory marker; ^b Risk for values above the median; OR: Odds Ratio; CI: confidence interval; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.

Table 3 - In-hospital mortality score among patients with acute myocardial infarction by logistic regression

Factors	Adjusted OR	CI (95%)	p-value	Coefficient β of logistic regression	Score* ($\beta \times 10$)
NLR					
< 3.7	1.0	-	-	-	0
≥ 3.7	4.28	1.30 - 14.1	0.017	1.455	15
NRBC					
Absence (0)	1.0	-	-	-	0
Presence (> 1)	10.1	4.06 - 24.9	< 0.001	2.308	23
MPV					
< 10,4	1.0	-	-	-	0
≥ 10.4	2.99	1.05 - 8.55	0.041	1.095	11

* Variation of points from 0 to 49 points; * The higher the score, the higher the risk of intrahospital death; OR: Odds Ratio; CI: confidence interval; NLR: neutrophil to lymphocyte ratio; NRBC: nucleated red blood cell; MPV: mean platelet volume.

with poorer prognosis. The scoring system with these three variables, after adjusted multivariate analysis and a cut-off of 26 points, showed a sensitivity of 89.1%, specificity of 67.2%, negative predictive value of 97.9% and positive predictive value of 26.8%. Thus, with these

cut-off points on a scale of 0 to 49 points, patients can be categorized into two groups: low and high risk of death, with an accuracy of 86.8% (area under the ROC curve). The main purpose of this hematological scoring system is to promote better clinical surveillance during hospitalization based on these laboratory variables. In addition, results of the score showed an agreement with patients' clinical data, as the lower risk in-hospital mortality was associated with lower score values. This hematological scoring system had a negative predictive value of 97.9%.

Table 4 - Sensitivity, specificity, positive predictive value and negative predictive value of the scoring system proposed using a cut-off of 26

Proposed scale of points	In-hospital Mortality	
	Yes	No
≥ 26 points	49	134
< 26 points	6	274

Validation measures	Percentage value	CI (95%)
Sensitivity	89.1%	0.809 – 0.973
Specificity	67.2%	0.626 – 0.717
Positive predictive value	26.8%	0.204 – 0.332
Negative predictive value	97.9%	0.962 – 0.996
C Statistic	86.8%	0.818 – 0.918

CI: confidence interval.

Table 5 - Relationship between the hematological scoring system and the KILLIP score in predicting mortality among patients with into ST-segment elevation myocardial infarction

Scale of points	KILLIP		Total
	I and II	III and IV	
≥ 26 points	120 (40.3%)	23 (82.1%)	143
< 26 points	178 (59.7%)	5 (17.9%)	183
Total	298	28	326

Kappa coefficient = 0.141 (61.5% overall agreement).

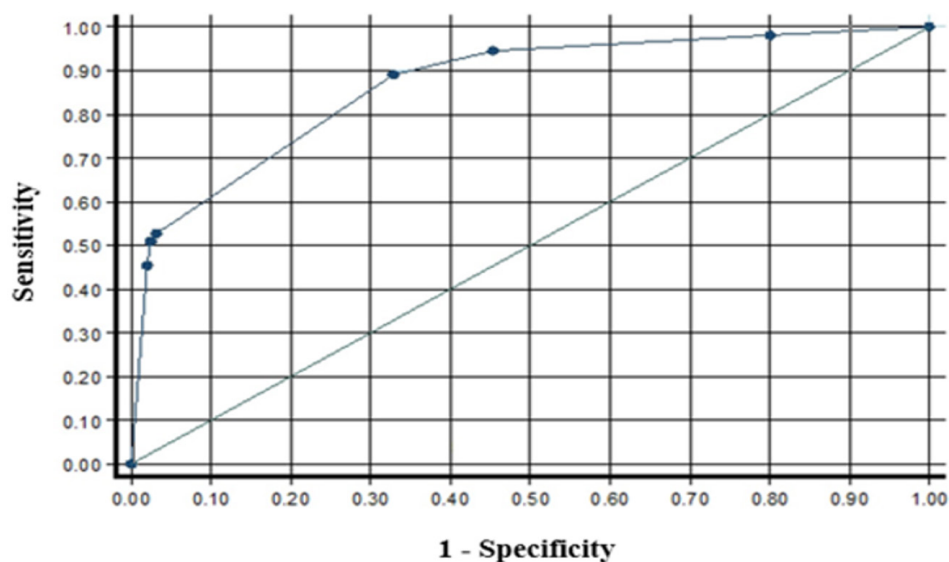


Figure 2 - ROC curve for the scoring system in predicting mortality. Area under the ROC curve = 0.868 (95% CI 0.818 - 0.918).

Table 6 - Relationship between the hematological scoring system and the TIMI RISK score in predicting mortality among patients with non-ST-segment elevation myocardial infarction

Scale of points	TIMI RISK		Total
	0 to 3	4 to 7	
≥ 26 points	8 (19.0 %)	35 (35.7%)	43
< 26 points	34 (81.0 %)	63 (64.3%)	97
Total	42	98	140

Kappa coefficient = 0.162 (50.7% overall agreement).

Patients with non-STEMI and STEMI were also classified as low risk (TIMI RISK 0 to 3 and Killip I and II) and high risk (TIMI RISK 4 to 7 and Killip III and IV), respectively, which facilitated the comparison with the hematological scoring system. In our sample, 70% of the patients had STEMI and 82.1% of these at high risk of mortality (Killip III and IV) had a score ≥ 26 points in the scoring system proposed. Also, 81% of the patients with non-STEMI at low risk of mortality (TIMI RISK 0 to 3) had a score < 26 points in the scoring system. Therefore, this new hematological scoring system could complement these extensively used risk scores in AMI patients. As mentioned before, the main purpose of this hematological scoring system is to improve clinical surveillance during hospitalization based on these laboratory variables, which would be of help in therapeutic decision making.

This hematological scoring system is dynamic, and changes in the risk profile may reflect the response to a treatment proposed. In this study, the instrument showed an 89.1% probability of identifying the outcome among those who died in this population. However, the hematological scoring system had a low positive predictive value (26.8%), probably due to the effective treatment employed. In this sample, 70% of these patients had STEMI and of these 43.9% had ≥ 26 points in the scoring system, and 30.7% of patients with non-STEMI had ≥ 26 points in the scoring system. In the present study, total mortality was 11.8% (55 patients): 43/326 (13.2%) STEMI and 12/140 (8.6%) non-STEMI.

Few studies have evaluated the performance of a scoring system including laboratory variables as a prognostic marker in AMI. Yanishi et al.,¹⁶ developed a simple stratification model using white blood cell count, hemoglobin, C-reactive protein, creatinine and

blood sugar levels for predicting in-hospital mortality in STEMI (ROC curve of the derivation and validation in laboratory model of 0.81 and 0.74 respectively, $p < 0.01$). A recent study by Ibrahim et al.,¹⁷ proposed a scoring system using clinical variables (male sex and previous percutaneous coronary intervention) and four biomarkers (midkine, adiponectin, apolipoprotein C-I, and kidney injury molecule-1) to predict with high accuracy the presence of obstructive coronary artery disease and mortality. In this study, elevated scores were predictive of ≥ 70% stenosis in all subjects (OR: 9.74; $p < 0.01$). At optimal cut-off, the score had 77% sensitivity, 84% specificity, and a positive predictive value of 90% for ≥ 70% stenosis. In another recent publication, Gerber et al.,¹⁸ demonstrated the importance of risk stratification for informed decision in clinical care.

The present study has some limitations. First, patients were selected in a single center. Second, heparin could inhibit platelet aggregation, but not platelet size. However, we increased the sample size, and used standardized and predetermined protocol to minimize possible bias.

Conclusions

The proposed hematological scoring system is a surveillance tool based on laboratory data, shown to be associated with in-hospital mortality in AMI patients. This simple and low-cost tool can be used to assess inflammation and hypoxemia caused by in-hospital complications using complete blood count parameters measured by an automated method. In addition, the scoring system is easy to use and interpret by all the multidisciplinary team members and can be calculated in the laboratory.

Further studies would help to confirm the usefulness and importance of this scoring system based on hematological laboratory parameters for clinical surveillance of inpatients with AMI.

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Author contributions

Conception and design of the research: Monteiro Júnior JGM, Torres DOC Silva MCFC. Acquisition of

data: Monteiro Júnior JGM, Torres DOC, Silva MCFC, Príncipe TRN, Vasconcelos RB, Brito MEC, Limeira MAA. Analysis and interpretation of the data: Monteiro Júnior JGM, Torres DOC, Santos ACO, Montarroyos UR, Sobral Filho DC. Writing of the manuscript: Monteiro Júnior JGM, Torres DOC, Santos ACO, Montarroyos UR, Sobral Filho DC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study is part of the project (Nucleated Red Blood Cells, Mean Platelet Volume and Neutrophil to Lymphocyte Ratio as Survival Biomarkers in Acute Myocardial Infarction) approved by the Ethics Committee in the HOSPITAL COMPLEX HUOC/PROCAPE of the University of Pernambuco under number CAAE: 51802115.7.0000.5192 (Brazil Platform). The research was conducted according to the principles of the Declaration of Helsinki.

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