

Prognostic Factors in Patients with Acute Coronary Syndrome without ST Segment Elevation

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Abstract

Background: In patients with acute coronary syndromes (ACS) without ST segment elevation (SSE), it is suggested that a series of markers (inflammatory cells, hyperglycemia and renal function) can identify individuals with increased risk for cardiovascular events.

Objective: To evaluate the impact of these laboratory parameters on intra-hospital outcomes of patients with ACS with no SSE.

Methods: We prospectively evaluated 195 patients consecutively admitted with ACS with no SSE. Demographic and clinical laboratory data were recorded during the course of the hospitalization period in relation to the occurrence of combined events.

Results: Mean age was 67 ± 12 years, and 52% were men. In analyzing the area under the ROC curve, only neutrophil/lymphocyte ratios (AUC: 70%, CI 95% 56%-82%, $p = 0.006$) and creatinine (AUC: 62%, CI 95% 50%-80%, $p = 0.03$) discriminated those patients with ACS with no SSE who presented an adverse outcome. The patients who suffered an adverse event during hospitalization had lower lymphocyte counts ($1502 \pm 731/\text{mm}^3$ vs. $2020 \pm 862/\text{mm}^3$; $p = 0.002$), lower glomerular filtration rates (51 ± 27 mL / min vs. 77 ± 34 mL/min; $p < 0,001$) and higher serum creatinine levels (2.1 ± 2.7 mg/dL vs. 1.1 ± 1.3 mg/dL; $p = 0.047$) than those who progressed through hospitalization without incident. The logistic regression analysis showed that variables remaining as independent and significant predictors were: glomerular filtration rate (OR: 1.03; CI 95%: 1.00 - 1.13, $p = 0.002$), and lymphocyte count (OR: 1.02; CI95%: 1.01 to 1.04, $p = 0.03$).

Conclusion: Assessment of renal function and lymphocyte count provide potentially useful information for the prognostic stratification in patients with ACS with no SSE (Arq Bras Cardiol. 2013; 100(5):412-421).

Keywords: Acute Coronary Syndrome; Hyperglycemia; Renal Insufficiency; Leukocyte Count.

Introduction

Acute coronary syndromes (ACS) without ST segment elevation (SSE) is a condition of high incidence¹, and the establishment of the risk of future events is critical in the evaluation and management of these patients. With this objective in mind, several prognostic markers were investigated. Inflammatory cells, hyperglycemia and renal insufficiency were considered promising and are easily accessible, since they are already part of the initial laboratory evaluation.

The presence of leukocytosis was associated with high mortality in patients with ACS without SSE²⁻⁴. Recently, however, an increase in the count of subpopulations of white cells was considered a better predictor of adverse events than leukocytosis. The presence of elevated neutrophils is

associated with a risk of death about six times higher⁵, and with the occurrence of reinfarction and rehospitalization for angina⁶. A low lymphocyte count was independently associated with mortality and myocardial infarction (MI)⁷. A new marker, the neutrophil/lymphocyte ratio (NRL), could integrate the predictive risk of these two types of white cells into a single prognostic factor, and it was considered superior to leukocyte count and its subtypes^{8,9}.

Another potentially useful variable in this scenario is the determination of glucose. Patients with ACS who have hyperglycemia on admission to hospital represent a high-risk population¹⁰, experiencing higher rates of reinfarction, recurrent angina, heart failure and cerebral vascular accident (stroke)¹¹, regardless of diagnosis of diabetes mellitus^{12, 13}.

Renal insufficiency has also been associated with the occurrence of adverse events in patients with SCA in several studies¹⁴⁻¹⁶. Severe renal insufficiency was associated with a four-fold higher intra-hospital risk of death in these patients¹⁴.

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Therefore, inflammatory cells, glucose levels and renal insufficiency are variables that have been highlighted in the literature; however, few of these studies have been carried out in our area. The objective of this study is to evaluate the importance of the previously mentioned laboratory parameters in assessing the prognosis of patients with ACS without SSE in a referral hospital for cardiology in Salvador, Bahia, Brazil. A secondary objective is to determine if invasive revascularization reduces the impact of predicting variables, compared with drug therapy.

Methods

Study design and sample selection

Consecutive patients admitted to the Emergency Ward and thereafter admitted to the Coronary Care Unit of the Hospital Português (Salvador, Bahia, Brazil) with a diagnosis of unstable angina (UA) or acute myocardial infarction (AMI) without SSE, from January to December 2010, participated in the study. We included those patients with chest pain or equivalent ischemic condition within 48 hours of admission and at least one of the three following characteristics: 1) ischemic electrocardiographic changes (T-wave inversion or ST segment depression), 2) serum markers of myocardial necrosis above the upper limit of normal, and/or 3) documentation of prior coronary artery disease. We excluded patients with: ST-segment elevation ≥ 1 mm in two or more leads on the admission ECG, normal coronary angiogram, hemodynamically significant primary valvular disease (mitral and aortic insufficiency or stenosis), hypertrophic cardiomyopathy, cancer, infectious diseases, autoimmune diseases and patients suffering from recent trauma or surgery.

This study was approved by the Ethics and Research Committee of Bahia School of Medicine and Public Health (*Escola Bahiana de Medicina and Saúde Pública*).

Study protocol and definitions

Blood samples for determination of blood glucose levels, inflammatory cell counts and serum creatinine were obtained at initial presentation to the emergency ward. The following data were evaluated: total white blood cell count, neutrophils, lymphocytes and NRL, blood glucose on hospital admission (GA), creatinine and glomerular filtration rate (GFR). Besides these variables, demographic data were also analyzed, as well as information regarding previous MI, comorbidities, smoking, body mass index (BMI), clinical presentation (UA or AMI without SSE), systolic function of the left ventricle (LV), levels of Troponin I (TnI) and CK-MB upon admission to the emergency ward, findings from coronarography and data from the revascularization strategy utilized.

The CellDyn 3700 hematology analyzer was used to determine the leukocyte count and its subtypes. Leukocytosis was defined as a leukocyte count $> 10,000$ cells/mL, neutrophilia as an absolute neutrophil count > 7000 cells/mL, and lymphocytopenia as an absolute lymphocyte count < 1500 cells/mL. The patients were divided into two groups according to the value of the NRL: those with NRL > 4.7 , and those with NRL ≤ 4.7 . This cutoff point was based on a previously published study.⁹

Creatinine was measured by the Jaffé colorimetric method (Dade-Behring, Newark, Delaware, USA)¹⁷. Creatinine clearance was calculated through Cockcroft-Gault's formula, defined as $[(140 - \text{age}) \times \text{weight kg} \times (0.85 \text{ if female})] / (72 \times \text{serum creatinine mg/dL})$ ¹⁸. Renal function was classified according to the definitions of the Kidney Disease Outcome Quality Initiative¹⁹.

Plasma glucose was determined enzymatically by the glucose oxidase method (Vitros 250 OrthoClinicalDiagnostics, Rochester, NY)²⁰. Hyperglycemia upon admission was defined as GA > 200 mg/dL.

The patient was considered diabetic, hypertensive or dyslipidemic if he confirmed having been informed of this diagnosis beforehand, or was using medication to control the disease.

The left ventricular systolic function was classified according to its ejection fraction, following the definitions recommended by the American Society of Echocardiography/European Association of Echocardiography²¹.

Obstructive coronary disease was considered any obstruction $\geq 70\%$, or $\geq 50\%$ if in the main left coronary artery, identified by coronarography. The patients treated with drug therapy were compared with those who had been revascularized by coronary angioplasty or myocardial revascularization surgery (MRS) during hospitalization.

Hospital outcomes

The intra-hospital outcomes studied were: non-fatal MI, recurrent UA, acute atrial fibrillation (AF), cardiogenic shock and death. Non-fatal MI was defined as the appearance of a Q wave or elevation of TnI during hospitalization, despite normal values during the first 24 hours. For patients who presented infarction at admission, a new peak CK-MB (greater than 50% than the previous value and above the normal value) was required for the diagnosis of reinfarction. An episode of angina at rest was defined as recurrent UA if one of the following criteria was present: physician's decision to administer sublingual nitrate or start intravenous nitrate, or need for urgent coronary angiography. For the diagnosis of acute AF during hospitalization, electrocardiographic evidence of an irregular rhythm maintained without atrial activation with no medical history of chronic atrial fibrillation was necessary. Cardiogenic shock was defined as systolic blood pressure (SBP) < 90 mmHg for at least 30 minutes, or the need for vasoactive support to maintain SBP > 90 mmHg during hospitalization.

Statistical analysis

Statistical analysis was performed with the SPSS program, version 14.0. Continuous variables are described as averages \pm standard deviation, and the dichotomous variables are presented as proportions. We used the Student *t* test, the χ^2 test and Fisher's exact test when appropriate. Values of $p \leq 0.05$ were considered significant.

The association between prognostic factor and outcome was determined using logistic regression analysis. The variables that presented $p < 0.10$ were considered in the multiple logistic regression model with manual deletion. Variables that remained in the model achieved significance ($p < 0.05$).

The ability of the variables to discriminate individuals at higher risk of adverse events was also assessed through the area under the ROC curve.

Results

Population characteristics

One hundred and ninety-five patients were studied in all. Mean age was 67 ± 12 years, and 52% ($n = 102$) were male. Sixty-nine percent of patients ($n = 134$) were diagnosed with UA and 31% ($n = 61$) with AMI without SSE. The demographic, clinical and laboratory characteristics of the patients are shown in Table 1.

The combined events occurred in 16.4% ($n = 32$) of the individuals (Table 2). Among the patients who died, one was diagnosed with UA (20%) and four with AMI without SSE (80%).

ROC curve analysis

Chart 1 shows the ROC curves for the variables NRL, blood glucose and serum creatinine in relation to the ability to identify outcomes.

According to ROC curve analysis, both NRL (area under the curve [AUC]: 70%, CI 95% 56%-82%, $p = 0.006$) and creatinine (AUC: 62%, CI 95% 50%-80%, $p = 0.03$) discriminated those patients with ACS with no SSE who presented an outcome. The curve of the glucose variable showed an AUC of 63% (95% CI: 51%-75%); however, it was only marginally significant ($p = 0.062$).

The AUC values of the three variables are shown in Table 3.

The variables of leukocytes, neutrophil and lymphocyte count, and GFR were also analyzed by the ROC curve. However, they were not found to be capable of discriminating those individuals at greatest risk.

Outcome occurrence in relation to the clinical and laboratory variables

The general characteristics in accordance with the occurrence of combined events are shown in Table 4. The patients who suffered an adverse event during hospitalization had lower lymphocyte counts ($1502 \pm 731/\text{mm}^3$ vs. $2020 \pm 862/\text{mm}^3$; $p = 0.002$), lower GFR (51 ± 27 mL/min vs. 77 ± 34 mL/min; $p < 0.001$) and higher serum creatinine levels (2.1 ± 2.7 mg/dL vs. 1.1 ± 1.3 mg/dL; $p = 0.047$) than those who underwent hospitalization with no incidents. White blood cell and neutrophil counts, NRL and GA did not show significantly different averages between the two groups of patients ($7781 \pm 3252/\text{mm}^3$ vs. $8140 \pm 2835/\text{mm}^3$, $p = 0.5$; $5653 \pm 3058/\text{mm}^3$ vs. 5220 ± 80 mg/dL, $p = 0.3$, respectively).

Lymphocytopenia (OR: 3.1; CI95%: 1.4-6.7; $p = 0.006$) and $\text{NRL} > 4.7$ (OR: 3.3; CI 95%: 1.4 to 7.6, $p = 0.006$) were more frequent in patients who had suffered an adverse outcome. In contrast, the presence of leukocytosis, neutrophilia and hyperglycemia was not statistically significant. The occurrence of adverse hospital events was more frequent in patients older than 65 years of age 75% vs. 54.6% (OR: 2.49; CI 95%: 1.06 to 5.88, $p = 0.049$) in comparison with those without complications.

There were no significant differences between the two patient groups with respect to: frequency of risk factors for coronary artery disease and comorbidities, left ventricular systolic function, and average CK-MB and Tnl values.

Thus, variables considered predictive in the univariate analysis were: lymphocyte count as a continuous and categorical variable, $\text{NRL} > 4.7$, serum creatinine levels, GFR and age greater than 65 years.

Table 5 shows the odds ratios of variables studied according to the occurrence of outcomes.

Independent predictors of intra-hospital outcomes

Those variables that had $p < 0.10$, or whose clinical relevance was already well documented, were included in the logistic regression model. The following variables were then selected from the univariate analysis: GFR; and age greater than 65 years, lymphocyte count and NRL as continuous variables.

The logistic regression analysis showed that the variables remaining as independent and significant predictors of increased mortality and of other clinical events were: GFR (OR: 1.03; CI 95%: 1.00 - 1.13, $p = 0.002$), and lymphocyte count (OR: 1.02; CI 95%: 1.01 to 1.04, $p = 0.03$).

Outcome occurrence in relation to treatment

A secondary interest of the study was to assess whether invasive revascularization reduces the impact of predictive variables on intra-hospital outcomes of patients with ACS but without SSE.

Patients who underwent invasive revascularization and had a $\text{GFR} < 60$ mL/min had a rate of adverse events similar to those patients with renal insufficiency who were offered drug therapy (44% vs. 56%, $p = 0.37$, respectively). Similarly, non-invasive revascularization was not associated with a lower risk of outcomes when compared with clinical treatment in patients with lymphopenia (41% vs. 59%, $p = 0.56$, respectively).

Discussion

In this study, GFR was considered a determining factor independent of intra-hospital adverse events in patients with ACS but without SSE. Recently, several prospective studies have demonstrated that reductions in GFR are associated with worse prognosis in various clinical situations. In patients with UA and AMI without SSE, renal insufficiency was a predictor of hospital mortality¹⁴ within 30 days¹⁶, and within 7 months¹⁵. In the GRACE study, moderate and severe reductions of GFR represented a two-fold risk and a four-fold risk of death, respectively²².

The mechanism by which a reduced GFR is associated with increased cardiovascular risk is probably related to the hemodynamic and metabolic changes, such as anemia, clotting alterations, proteinuria and homocysteinemia observed in this condition²³. In addition, in most of the studies, reductions in GFR are related to a higher frequency of risk factors for DCV^{14, 15, 24}, which by itself could pose a higher risk of adverse events in patients with ACS.

Table 1 – Clinical and laboratory characteristics of patients (n = 195)

Variable	Description
Age (years)	67 ± 12
Male	102 (52%)
IMC (>30 Kg/m ²)	48 (24.6%)
Smoking	21 (10.8%)
HAS	170 (87.2%)
Diabetes	80 (41%)
Dyslipidemia	96 (49.2%)
Peripheral vascular disease	10 (5.1%)
Cerebrovascular disease	13 (6.7%)
Previous MI	46 (23.6%)
Diagnosis	
UA	134 (68.7%)
AMI without SSE	61 (31.3%)
Systolic Function of the Left Ventricle	
Normal (EFLV ≥55%)	168 (86%)
Mild dysfunction (EFLV between 45%-54%)	9 (4.6%)
Moderate dysfunction (EFLV between 30%-44%)	5 (2.6%)
Severe dysfunction (EFLV < 30%)	4 (2%)
Value of CK-MB	4.7 ± 18.7
Value of TnI	0.760 ± 3.880
Total leukocyte count (cells/mL)	8082 ± 2900
Total neutrophil count (cells/mL)	5290 ± 2590
Lymphocyte count (cells/mL)	1937 ± 862
NRL	3.8 ± 4.4
Leukocytosis (>10.000 cells/mL)	36 (18.5%)
Neutrophils (>7.000 cells/mL)	36 (18.5%)
Lymphocytopenia (<1.500 cells/mL)	63 (32.3%)
NRL > 4.7	38 (19.5%)
Glucose (mg/dL)	138 ± 79
Hyperglycemia (>200 mg/dL)	20 (10.3%)
Renal Function	
Serum creatinine (mg/dL)	1.3 ± 1.6
Creatinine clearance (mL/min)	73 ± 34
GFR < 60 mL/min	67 (34.4%)
Coronaryography	138 (70.8%)
Presence of obstructive CAD	104 (53.3%)
Coronary angioplasty	58 (29.7%)
Revascularization surgery	8 (4.1%)

Data are shown as averages ± standard deviations, or n (%). UA: Unstable Angina; CAD: Coronary Artery Disease; PVD: Peripheral Vascular Disease; EFLV: Ejection Fraction of the Left Ventricle; AMI without SSE: Myocardial Infarction without ST Segment elevation; MI: Myocardial Infarction; BMI: Body Mass Index; SAH: Systemic Arterial Hypertension; NRL: Neutrophils/Lymphocyte Ratio; GFR: Glomerular Filtration Rate; TnI: Troponin I.

Table 2 – Intra-hospital Outcomes (n = 32)

Outcomes	Frequency
Death	5 (2.6%)
Recurrent UA	18 (9.6%)
Acute AF	10 (5.1%)
Cardiogenic Shock	6 (3.1%)
Non-fatal MI	4 (2.1%)

UA: Unstable Angina; AF: Atrial Fibrillation; MI: Myocardium Infarction.

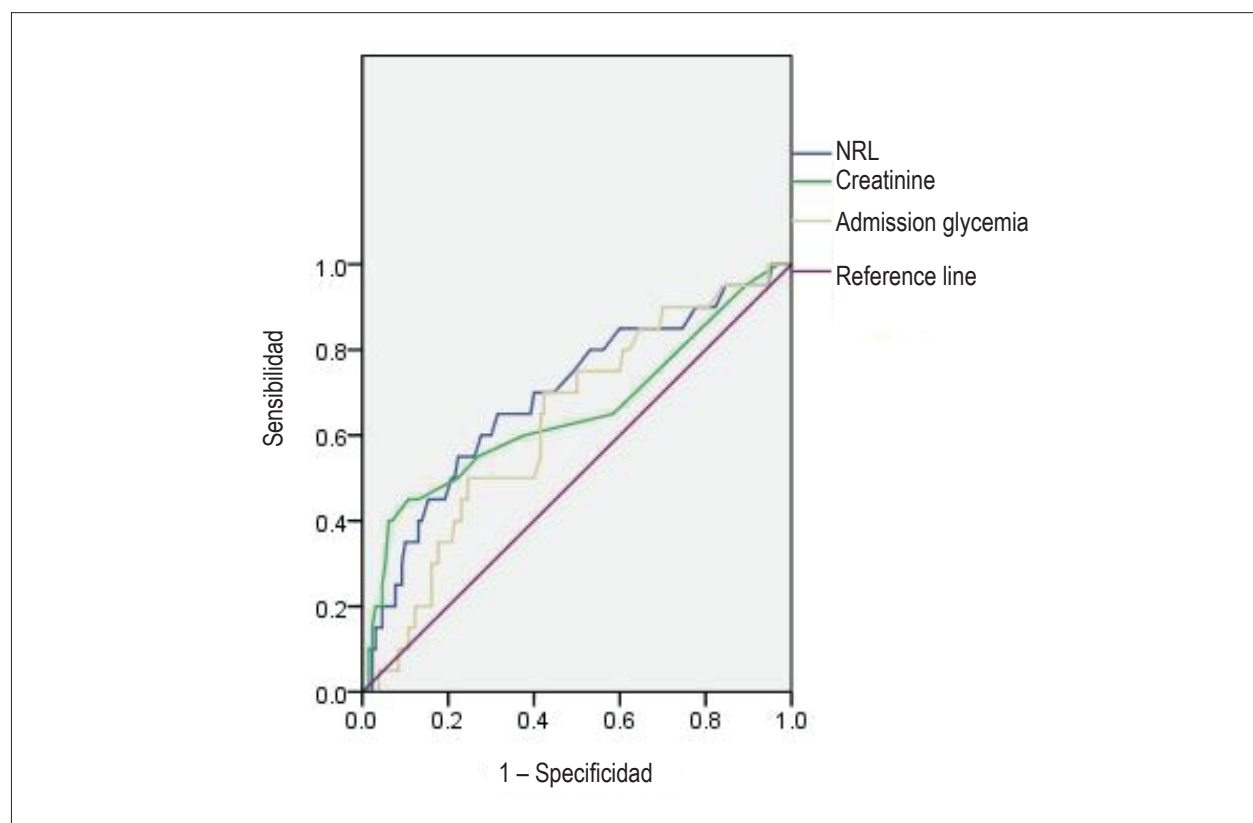


Chart 1 - ROC Curve of the three variables studied. NRL: Neutrophil/Lymphocyte Ratio.

Table 3 – Areas under the ROC (AUC) curves, confidence intervals (CI) and p values of NRL variables, glucose and serum creatinine

Variables	AUC	IC95%	p
NRL	0.7	0.56 – 0.82	0.006
Glucose	0.63	0.51 – 0.75	0.062
Serum Creatinine	0.65	0.5 – 0.8	0.03

NRL: Neutrophil/Lymphocyte Ratio.

Table 4 – Characteristics of the population according to the occurrence of the combined events

Variables	Combined Events		p
	Yes (n = 32)	No (n = 163)	
Age > 65 years (n = 113)	24 (75%)	89 (54.6%)	0.049
Male (n = 102)	19 (59.4%)	83 (50.9%)	0.44
SAH (n = 170)	29 (90.6%)	141 (86.5%)	0.77
Dyslipidemia (n = 96)	18 (56.3%)	78 (47.9%)	0.44
Diabetes Mellitus (n = 80)	15 (46.9%)	65 (39.9%)	0.56
Smoking (n = 21)	4 (12.5%)	17 (10.4%)	0.76
Family History of CAD (n = 21)	2 (6.3%)	19 (11.7%)	0.54
BMI	27.1 ± 4.9	26.8 ± 5.2	0.78
Previous MI (n = 46)	8 (25%)	38 (23.3%)	0.82
Cerebrovascular Disease (n = 13)	4 (12.5%)	9 (5.5%)	0.23
PVD (n = 10)	2 (6.3%)	8 (4.9%)	0.67
Systolic Function of the Left Ventricle			
Normal (n = 168)	25 (78%)	143 (87.7%)	0.16
Mild dysfunction (n = 9)	3 (9.4%)	6 (3.7%)	0.17
Moderate dysfunction (n = 5)	2 (6.3%)	3 (1.8%)	0.19
Severe dysfunction (n = 4)	1 (3.1%)	3 (1.8%)	0.51
Value of CK-MB	5.4 ± 18.3	4.6 ± 18.8	0.83
Value of Tnl	1.006 ± 4.800	0.174 ± 3.696	0.71
NRL > 4.7 (n = 38)	12 (38.7%)	26 (16%)	0.006
GFR < 60 mL/min (n = 67)	16 (50%)	51 (31.3%)	0.065
Hyperglycemia (n = 20)	4 (20%)	16 (12.2%)	0.31
Total leukocyte count (cells/mL)	7780 ± 3251	8140 ± 2835	0.53
Total neutrophil count (cells/mL)	5652 ± 3057	5220 ± 2496	0.4
Lymphocyte count (cells/mL)	1502 ± 731	2020 ± 862	0.002
NRL	5.0 ± 4.4	3.5 ± 4.3	0.07
AG (mg/dL)	153 ± 71	136 ± 80	0.35
Serum creatinine (mg/dL)	2.1 ± 2.7	1.1 ± 1.3	0.047
GFR (mL/min)	51 ± 27	77 ± 34	< 0.001

Data are shown as averages ± standard deviation, or n (%). CAD: Coronary Arterial Disease PVD: Peripheral Vascular Disease; MI: Myocardial Infarction; BMI: Body Mass Index; AG: Admission Glucose; SAH: Systemic Arterial Hypertension; NRL: Neutrophils/Lymphocyte Ratio; GFR: Glomerular Filtration Rate; Tnl: Troponin I.

Elevations in serum creatinine levels were associated with an increased risk of adverse events in this study ($p = 0.047$ in univariate analysis). This variable was also considered a predictor ($p = 0.03$) in the ROC curve analysis, despite its modest discriminative capacity (AUC of 65%). Fácila et al²⁵ demonstrated that the determination of creatinine has great importance for the initial stratification of patients with ACS without SSE, and a predictive capacity similar to GRF (CI = 0.81 for both variables).

Thus, assessment of renal function, both by serum creatinine and by the GFR, seems to provide valuable information for intra-hospital risk stratification in patients with ACS without SSE.

In the multivariate model, the lymphocyte count was also associated with an increased risk of adverse outcomes. It has been well documented that inflammation plays a crucial role in atherosclerosis. For prognostic purposes, clinical research has focused on the leukocyte count as a whole, as well as neutrophils and C-reactive protein. However, little is known about the role of lymphocytes, which play an important role in controlling the inflammatory system and the pathophysiology of CAD (coronary artery disease). Núñez et al⁷ found that in patients with UA, only lymphocytes, among the subtypes of white blood cells, were associated with death and MI during a follow-up period of five years. Dragu et al⁶ in a study of 1307 patients with MI

Table 5 – Odds Ratio (OR) and Confidence Interval (CI) of the variables studied for the occurrence of intra-hospital outcomes

Variable	OR (95%CI)	p
Age > 65 years old (n = 113)	2.49 (1.06 – 5.88)	0.049
Male (n = 102)	1.4 (0.65 – 3.04)	0.44
SAH (n = 170)	1.5 (0.42 – 5.375)	0.77
Dyslipidemia (n=96)	1.4 (0.65 – 3.0)	0.44
Diabetes Mellitus (n = 80)	1.3 (0.62 – 2.85)	0.56
Smoking (n = 21)	1.2 (0.38 – 3.9)	0.76
Family History of CAD (n = 21)	0.5 (0.1 – 2.285)	0.54
Previous MI (n = 46)	1.1 (0.455 – 2.64)	0.82
Cerebrovascular Disease (n = 13)	2.4 (0.7 – 8.49)	0.23
PVD (n = 10)	1.3 (0.26 – 6.385)	0.67
Systolic Function of LV		
Normal (n = 168)	0.5 (0.19 – 1.3)	0.16
Mild dysfunction (n = 9)	2.7 (0.64 – 11.4)	0.17
Moderate dysfunction (n = 5)	3.6 (0.57 – 22.19)	0.19
Severe dysfunction (n = 4)	1.7 (0.17 – 17.1)	0.51
Leukocytosis (n = 36)	0.8 (0.3 – 2.3)	0.81
Neutrophils (n = 36)	1.1 (0.4 – 2.8)	1.0
Lymphocytopenia (n = 63)	3.1 (1.4 – 6.7)	0.006
NRL > 4.7 (n = 38)	3.3 (1.43 – 7.62)	0.006
Hyperglycemia (n = 20)	1.8 (0.534 – 6.05)	0.31
GFR < 60 mL/min (n = 67)	2.2 (1.0 - 4.7)	0.065

CAD: Coronary Artery Disease; PVD: Peripheral vascular disease; MI: Myocardial infarction; SAH: Systemic arterial hypertension; NRL: Neutrophil/Lymphocyte Ratio; LV: Left Ventricle; GFR: Glomerular Filtration Rate.

(68% had ST elevation), reported that lymphocytopenia was independently associated with mortality in the long term. Horne et al²⁶ extended these results to patients with both stable and unstable angina.

It has not yet been explained whether this association is causal or is simply a marker of myocardial and microvascular injury. The most accepted explanation is that lymphocytopenia reflects acute stress, secondary to release of cortisol⁷. In an alternative model, in ACS, the immune system would be acutely deregulated, causing loss of regulatory T-cells and a consequent pro-inflammatory condition, with the clearance of cytokines and dislocation of monocytes and neutrophils to the ischemic site²⁷.

In this study, we found that the total white cell count and the total count of neutrophils were not able to discriminate those patients with increased risk of adverse events. Leukocytosis and neutrophilia were associated with an increased risk of death in ACS²⁻⁵. On the other hand, in Cannon et al.'s study²⁸, this relationship was only true in infarcted patients; in those with UA, this relationship did not reach statistical significance. Lloyd-Jones et al²⁹ reported that in patients with UA, leukocytosis was not associated with intra-hospital outcomes, including recurrent angina, MI and revascularization. In a population of 71 patients with

UA, a low lymphocyte count was associated with a high risk of future cardiac events³⁰. There was no association between the white cell count or neutrophil count with the events. Similarly, Nuñez et al⁷ demonstrated that in patients with acute chest pain, non-diagnostic ECG and no elevation of troponin, no other subpopulation of leukocytes was associated with myocardial infarction or death, including lymphocytes. According to these data, the white cell count and neutrophil count appear to be good prognostic markers in patients with UA. In this population, the lymphocyte count probably best identifies those at greatest risk.

In this study, 69% of the patients (more than two-thirds of the sample) were diagnosed with UA, which may explain the results found. Furthermore, due to the relatively small sample size, the study may have limited power to detect an association between leukocytosis and neutrophilia and outcomes.

In this study, we found that the patients who had a high NRL had a higher proportion of complications, with p tending towards significance (p = 0.07). The patients with NRL > 4.7 presented approximately a two-fold risk of suffering combined outcomes (p = 0.006 in univariate analysis). In agreement with these results, in the ROC curve analysis, the NRL was also a predictor of intra-hospital events. It has been shown previously that this variable is

independently associated with a worse prognosis in the short and long term in all manifestations of ACS^{8,9}. In our study, however, the association between NRL and outcomes lost significance when it was added to the multivariate analysis.

With respect to the GA, the patients who suffered a complication had average blood glucose higher than those who had no complications during hospitalization; however, this relationship was not significant. In the ROC curve, the GA was not capable of discriminating the patients at higher risk. The results of this study are divergent with the literature, which consistently showed that acute hyperglycemia is an important marker in the context of ACS^{10,12,13}. Patients with high GA present a 22% higher death risk than normoglycemic patients³¹. Ishihara et al¹¹ showed that, in terms of hospital mortality, hyperglycemia upon admission is a more important risk marker than a previous history of diabetes mellitus. Müdespacher et al¹⁰ found that for each increase of GA by 1 mmol/L, there was an 8% increase in the risk of intra-hospital death. The difference between our results and the studies mentioned here is probably due to the small size of the study population; however, we cannot exclude that the differences between these populations may also interfere in the results.

Recent guidelines support the interventionist strategy (coronary angiography and intervention as soon as possible, ideally within 24 hours of admission) to reduce recurrent ischemia in patients of intermediate or high risk with ACS without SSE³². However, in some high-risk subgroups, such as the very old, with renal insufficiency or with cardiac insufficiency, the benefit of early invasive revascularization remains controversial. Several variables were associated with a worse prognosis in this context, but a few also have therapeutic implications.

Patients with impaired renal function are less likely to receive therapies known to improve evolution of ACS during hospitalization²². In addition, these patients are often excluded from randomized controlled clinical studies³³, or represent only a small percentage of patients in observational studies³⁴. Thus, it remains uncertain if these patients have a better prognosis when managed with invasive revascularization in addition to drug therapy. In those with severe renal insufficiency or on dialysis, the interventionist strategy seems to be harmful³⁵.

To date, only one study evaluated the therapeutic implications of lymphopenia in patients with ACS without SSE. Núñez et al³⁶ demonstrated that a low lymphocyte count is a marker of high risk for patients with ACS without SSE, and the interventionist strategy in this context reduces the risk of non-fatal MI in the long term (three years). The authors suggest that the availability and low cost of this biomarker make it a promising tool for risk stratification and in choosing a revascularization strategy for these patients.

In the present study, invasive revascularization did not reduce the risk conferred by renal insufficiency or lymphopenia, compared with drug therapy.

This study has some limitations. Besides the sample size, this was a single-center study, thus its results cannot be fully extended to other populations. Moreover, this is an observational study and therapeutic strategies were not randomized, which could lead to a selection bias.

In conclusion, the main finding of this study is that the estimation of renal function and lymphocyte count are independent predictors of intra-hospital adverse events in our patient population with ACS without SSE.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Obtaining funding and Writing of the manuscript: Santos JCMD, Rocha MS; Acquisition of data: Santos JCMD, Araújo MS; Critical revision of the manuscript for intellectual content: Rocha MS.

Potential Conflict of Interest

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

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