

Predictive Utility of Morbidity and Early Mortality of the Neutrophil to Lymphocyte Ratio in Patients with Acute Coronary Syndrome

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Abstract

Background: In recent years, the role of inflammation as predictor of ongoing outcomes of infectious and systemic diseases has been described. The neutrophil/lymphocyte ratio (NLR) has been described with good predictive value of complications, few data are available in the course of cardiovascular disease, some studies describe the utility in patients in the course of cerebrovascular disease.

Methods: We conducted an descriptive, observational, prospective study to evaluate the utility of the neutrophil-lymphocyte ratio as predictor of early mortality in patients during the course of an acute myocardial infarction. We include 65 clinical files of patients entitled to ISSSTE who have completed their stay in the coronary intensive care unit of the National Medical Center November 20

(ISSSTE) in the period from January 1, 2017 to January 1, 2018. The primary point of the study was to evaluate the relationship between and elevated NLR and death or acute heart failure in the first 48 hours, 1 week, 3 months after the event.

Results: There is a direct relationship between the INL value and in-hospital mortality, We suggest a cutoff point ≥ 4.32 with a sensitivity of 100% and specificity of 51.9%, and a cut-off point ≥ 4.4 as a predictor of major cardiovascular adverse events (MACE) and fatal arrhythmias.

Conclusions: There's growing evidence of the important of the inflammation status in outcomes in patients in the course of and cardiovascular event: acute myocardial infarction.

We propose the NLR as an new tool, even to add to scores like TIMI (The Thrombolysis in Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Event).

Keywords: *Acute Coronary Syndrome; Neutrophil/Lymphocyte Ratio; Mortality; Mayor Adverse Cardiovascular Events; ST-Elevation Myocardial Infarction; Non-ST Elevation Myocardial Infarction*

Introduction

Acute coronary syndrome manifests itself in the form of acute myocardial infarction or unstable angina, the most dangerous form is the "acute myocardial infarction with persistent ST elevation), representing the world's leading cause of morbidity and mortality. In Mexico, the most recent registry: RENASICA III (National Registry of Acute Coronary Syndromes) which included more than 8'000 patients, in which ischemic coronary disease was confirmed as the main cause of death in older adults and second cause in the general population, In 2011, 71,072 deaths associated with acute coronary syndrome were recorded, corresponding to 11% of all causes in our country [1-4].

This cardiological condition is closely related to chronic atherosclerosis, which in the past was considered a non-inflammatory disease. Now we know that this a Dynamic process where various factors involved, and inflammatory processes played an essential role. In this chronic disease, the vascular target is essentially the endothelial dysfunction at the microvascular level (Nitric oxide decrease, Von Willebrand factor increase and vascular endothelial growth factor) and macro-vascular (vessel dilation), which favor the precipitation of lipids and formation of the atherosclerotic core and plaque [3,5-7].

The determination of circulating leukocytes in peripheral blood is a method that allows to evaluate the presence of acute and chronic inflammation. The ratio between the absolute number of neutrophils and the absolute number of lymphocytes (neutrophil/lymphocyte ratio) is significantly associated with cytokine levels and inflammatory diseases, as well as with morbidity and mortality in patients with cerebral infarction, colon cancer advanced, acute cholecystitis and pancreatitis [8-10].

In the course of an acute myocardial infarction a severe inflammatory process is triggered, with significant elevation of inflammatory cells and biomarkers, which initiation and amplification of negative pathophysiological circles that feed the inflammatory cell chemotaxis. In a population that suffers from acute cerebral ischemic events, the neutrophil/lymphocyte ratio (NLR) has shown a close relationship with morbidity and mortality, as well as a significant association with the elevation of inflammatory markers [11-13].

In patients with acute coronary syndrome, we can detect a significant elevation of various inflammatory markers with different prognostic utility of early mortality have been found, highlighting the levels of Reactive Protein C, interleukin 6 and Tumor Necrosis Factor. Reactive leukocytosis has also been observed in inflammatory processes related to endothelial lesion and myocardial necrosis [8,9].

The Neutrophil-Lymphocyte ratio (NLR) is an easy measurement to perform and requires basic infrastructure, which is accessible in most secondary and tertiary health care hospitals, so it is considered that it could be useful for predicting morbidity and mortality in patients with acute coronary syndrome, which could identify an easily accessible diagnostic tool that allows a better stratification of patients suffering from this heart disease [14,15].

Methodology

Trial population

We conducted a descriptive, observational, prospective, single-center study. In which the patients of the Coronary Intensive Care Unit of the “National Medical Center November 20” admitted with a diagnosis of acute coronary syndrome were included; Infarction with elevation of the ST segment and infarction without elevation of the ST segment during the period from January 1, 2017 to January 1, 2018.

Determination of cardiac haemodynamics (by using echocardiography with equipment IE33 - Phillips) was necessary and performed within 24 hours after patient admission to evaluate the requirement of vasoactive and inotropic agents. The quantification of blood biometrics was also performed within 24 hours after admission.

We determinate the levels of procalcitonin at the admission and perform urine analysis to exclude infectious causes of shock. Patients with previous rheumatologic disease were also excluded.

Statistical analysis

Data were collected in the Excel program in version 354 and the SPSS program in version 22 was used to calculate descriptive statistics, frequency and statistical associations. Qualitative variables are reported in frequency and percentage and quantitative variables with measures of central tendency such as the average. A 95% confidence interval was considered and as significant $p \leq 0.05$.

Chi² (Fisher’s test) was used to associate the qualitative variables and Student’s t to compare the quantitative variables.

We follow patients after acute myocardial infarction during a period of three months, and with a determination of left ventricle ejection fraction after 6 weeks of the event was performed.

ROC curve was performed to determinate the relationship between the NLR and mortality, acute heart failure, and long hospital stay.

Results

During the period from January 1, 2017 and January 1, 2018, 90 patients with a diagnosis of acute coronary syndrome were reported: of which 80 were used for statistics: 15 had a definitive diagnosis different from acute coronary syndrome (elevation infarction of ST, infarction without ST elevation, right ventricle infarction).

During the study, there were a total of 65 patients diagnosed with acute coronary syndrome; which were divided into 3 main categories: acute myocardial infarction with ST segment elevation (whose group corresponded to 45% of the total sample), non-ST segment elevation infarction (47.7% of the total sample) and infarction of the myocardium with involvement of the right ventricle (10.8% of the total sample). The predisposition of sex was for the male gender with a total of 74% of the total (48 patients) (Table 1). Patients distribution by acute coronary syndrome type were organized in table 2.

| Characteristic | N = 65 Distribution |
|--|---------------------|
| Age (years) | 66.2 ± 8.38 |
| Hospitalization days | 7.78 ± 9.64 |
| Gender | |
| Female | 48 (74%) |
| Male | 17 (26%) |
| Diagnosis | |
| Non-ST elevation myocardial infarction | 31 (48%) |
| ST elevation myocardial infarction | 27 (41%) |
| Right ventricle infarction | 7 (11%) |

Table 1: Characteristics of the patients included in the study.

| | | Non ST elevation myocardial infarction | ST elevation myocardial infarction | Right ventricle infarction | Total |
|--------|--------|--|------------------------------------|----------------------------|-------|
| Gender | Male | 20 (30.7 %) | 22 (33.8 %) | 6 (9.25 %) | 48 |
| | Female | 11 (17 %) | 5 (7.7 %) | 1 (1.55 %) | 17 |
| Total | | 31 (47.7%) | 27 (41.5 %) | 7 (10.8 %) | 65 |

Table 2: Percentual distribution according to the type of acute coronary syndrome by gender.

Cardiovascular risk factors in the study groups were organized, the most common factor was Systemic artery Hypertension which represents a total of 73.84% in all the three groups; followed by dyslipidemia in 49.2% (32 patients in all the groups), type 2 diabetes mellitus (T2-DM) was the less common major cardiovascular risk factor in a total of 44.4%. The distribution of the Major cardiovascular risks is organized in table 3.

| | Non-ST elevation myocardial infarction (31 patients) | ST elevation myocardial infarction (27 patients) | Right ventricle infarction (7 patients) |
|--------------------------------|--|--|---|
| Dyslipidemia | 48.38% | 44.4% | 71.42% |
| Systemic Artery Hypertension | 77.4% | 66.6% | 85.71% |
| Previous myocardial infarction | 6.45% | 7.4% | 28.57% |
| Tabaquism | 38.7% | 18.5% | 28.5% |
| Type-2 Diabetes mellitus | 41.93% | 40.74% | 71.42% |

Table 3: Distribution of major risk factors according to the type of acute coronary syndrome.

Table 4 summarizes the arrhythmias documented during the study, it is observed that the group with the highest development of arrhythmias was the right ventricle infarction group with a total of 85.7% for their study group, subsequently acute myocardial infarction with elevation of the ST segment showed a total of 13 events, of which the most predominant was atrial fibrillation 25.9% of the corresponding group. With VT (Ventricular tachycardia) being the arrhythmia with the highest occurrence in the patient groups, an-ROC curve was performed for NLR sensitivity in relation to TV development (Figure 1).

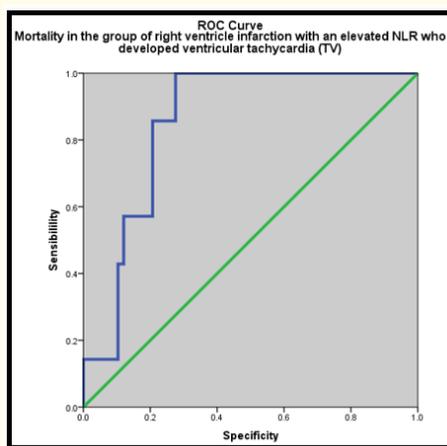


Figure 1: Relationship between development of ventricular tachycardia in the group of patients in the course of right ventricle infarction.

| | | Non-ST elevation myocardial infarction | | | ST-elevation myocardial infarction | | | Right ventricle infarction | | |
|------|------------------------|--|--|---|------------------------------------|-----------------------------------|---|----------------------------|-----------------------------------|---|
| | | Total | % of the total amount of patients (65) | % of the patients with Non-ST elevation myocardial infarction | Total | % of the total amount of patients | % of the patients with ST-elevation myocardial infarction | Total | % of the total amount of patients | % of the patients with right ventricle infarction |
| MACE | Number | 24 | 36.9% | 77.4% | 19 | 29.2% | 70.4% | 1 | 1.5% | 14.3% |
| | Positive | 7 | 10.8% | 22.6% | 8 | 12.3% | 29.6% | 6 | 9.2% | 85.7% |
| | Cerebrovascular event | 3 | 4.6% | 9.7% | 3 | 4.6% | 11.1% | 0 | 0.0% | 0.0% |
| | New infarction | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% |
| | Sudden death | 0 | 0.0% | 0.0% | 3 | 4.6% | 11.1% | 3 | 4.6% | 42.9% |
| | Acute heart failure | 3 | 4.6% | 9.7% | 2 | 3.1% | 7.4% | 3 | 4.6% | 42.9% |
| | Acute stent thrombosis | 1 | 1.5% | 3.2% | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% |

Table 4: Distribution of the type of MACE according to infarction type.
MACE: Major Adverse Cardiovascular Event.

In the MACE category, there was no predisposition for the total sample in the different types of MACE, a predisposition was shown within the independent groups, the cerebrovascular event and acute heart failure as the main manifestations; while in the group of ST elevation infarction increase is the same number of events (3, corresponding to 4.6% of the total and 11.1% of the group) in relation to cerebrovascular event and sudden death.

In terms of death and acute heart failure, we organize the groups according to the type of acute coronary syndrome, we can observe a major number of death and acute heart failure as in the arrhythmias evaluation in patients with right ventricle infarction, followed by ST-elevation myocardial infarction group with a total of 11.1% of deaths of the amount of patients in the group.

In terms of acute heart failure ST-elevation myocardial infarction patients with a NLR > 3.90 was directly associated with development of severe heart failure in all the groups, this predisposition was very striking in the right ventricle infarction group, followed by ST - elevation myocardial infarction, the 3.90 cutoff value have an area under the curve of 0.80, sensitivity of 95% and specificity of 52.3% and an statistic P value of < 0.05 to cardiogenic shock development in the acute coronary syndrome patients (Figure 2).

In the evaluation of the primary outcome, we made an estimate to assess the correlation between mortality and NLR, we found that a cutoff value of 4.32 with a strong predictive value, sensitivity of 100% and specificity of 51.9% to predict mortality in hospitalization of patients with acute coronary syndrome, as we've shown before, this predictive correlation is higher in patients with right ventricle infarction.

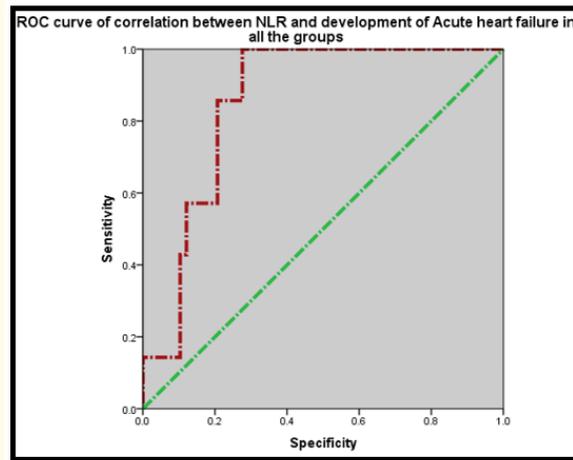


Figure 2: A close correlation was found, with an area under the curve of 0.802, with statistical significance of < 0.001 , and it was found that for this group of patients (cardiogenic shock), a value ≥ 3.90 has a sensitivity of 95% and specificity of 52.3 % to predict development of cardiogenic shock.

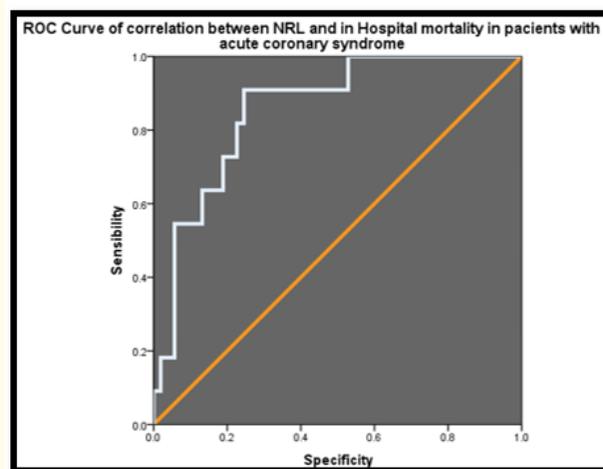


Figure 3: ROC curve of correlation between the value of NLR and hospital death. It is observed that the curve is above the line, with an area under the curve of 0.86 and whose significance was < 0.001 .

Discussion

With a total of 65 patients diagnosed with acute coronary syndrome: including Non-ST elevation myocardial infarction, ST-elevation myocardial infarction and right ventricle infarction and classifying as infarction according to the fourth universal definition over the course of 12 months, the distribution It was similar for the NST-EMI and S-EST groups, therefore analysis was performed to assess data asymmetry, with adequate validation of data for the 3 groups, so descriptive statistics were subsequently performed to assess frequencies, risk factors.

The predominant group was Non-ST elevation myocardial infarction with a total of 48% (31 cases of the total sample), followed by ST-elevation myocardial infarction with 41% (28 cases of the total sample) and 11% (7 cases total sample) for the right ventricle infarction group.

Mortality according to the groups was predominantly of the right ventricle group, when performing the analysis it was found that a value > 4.32 was correlated with hospital mortality, with a sensitivity of 100% and specificity of 51.9%, being in the subgroup analysis a similar value, compared to other studies, the largest of these was recently published in JAMA, where it was found for a population of Jackson, Mississippi, evaluated in African-American people, where it was found that a value ≥ 2.15 that was associated during follow-up With the development of cardiovascular death, no data was found in this regard for patients in the course of acute coronary syndrome, however, this is the largest study published for the purpose of study in cardiovascular diseases [16].

On the other hand, an associated relationship was found for the development of major cardiovascular events, finding for this group a ≥ 4.4 , a sensitivity of 85.7% and 51.7% specificity was found to predict MACE in this group of patients. In other studies, several are found with similar numbers to ours, in a meta-analysis performed with 8 of them, a similar value (≥ 5) is found to predict mortality in patients with acute coronary syndrome, which correlates with the published bibliography However, this is the first record in Mexico for this group of patients [17,18].

In the total of patients, the main cause of death was the development of MACE, mainly heart failure and arrhythmias, of which ventricular tachycardia (TV) was the most associated to this, it was performed given the similarity of the groups, for what that a value ≥ 4.4 was found as a predictor of TV development in patients with ACS, with a sensitivity of 85.7% and a specificity of 51.7% to predict its occurrence, no data are found in the current literature for the risk of Arrhythmias in these patients, however, have been included in some studies as part of the MACE group.

In the current bibliography, there are no data available with specific tools to predict mortality in specific groups, such as right ventricular infarction, since it is a rare entity, however, its high mortality is known in all possible scenarios. In our group, a direct relationship of INL for death development was found, with an area under the curve of 0.85, 100% sensitivity and 50% specificity for a value ≥ 4.4 , however, a larger number of patients is required to be able to find an adequate relationship with respect to this group of patients.

Conclusion

There's growing evidence of the important of the inflammation status in outcomes in patients in the course of and cardiovascular event: acute myocardial infarction, cerebrovascular accident or peripheral embolism. The neutrophil to lymphocyte ratio is an easy, quickly and reproducible tool that is very helpful to evaluate the inflammatory status and its role in outcomes in patients with acute myocardial infarction to predict heart failure (cardiogenic shock), arrhythmias and in hospital mortality (specially in the groups with acute right ventricle infarction).

We propose the NLR as a new tool, even to add to scores like TIMI (The Thrombolysis in Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Event).

Conflicts of Interest

There is no conflict of interest in this article.

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