UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA",

BUCHAREST

DOCTORAL SCHOOL MEDICINE FIELD

Ph.D. THESIS SUMMARY

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New predictive factors in patients with acute myocardial infarction

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GENERAL PART-INTRODUCTION

Cardiovascular diseases account for 1/3 of global mortality and Ischemic coronary heart disease is responsible for 7.5 million deaths, twice the rate of deaths caused by neoplasms. [1]

The high mortality rate is mainly caused by conditions such as Acute Coronary Syndrome (ACS) and sudden cardiac death, which cause approximately 1.8 million deaths per year. Cardiovascular diseases account for 126.5 million cases per year, representing approximately 44% of deaths caused by noncommunicable diseases (WHO, 2021). [2]

The risk stratification strategy in these patients is crucial.

Most of the stratification scores for patients with ACS were developed in 2009-2017. Without a doubt, these scores have helped to manage patients with ACS in the most efficient and beneficial way.

However, without trying for a second to deprive them of their major role, these scores include markers that are not available in the first minutes of presentation, do not involve male/female differentiation and do not take into account the inflammatory process. Thus, these scores were developed on a traditional statistical model, excluding the inflammatory stage, essential from the point of view of the evolution and management of the patient with ACS. [3]

Recently, the GRACE 3.0 score was updated to reduce gender differences. However, it was specifically designed for patients with non-ST-segment elevation myocardial infarction (NSTEMI), excluding patients with ST-segment elevation myocardial infarction (STEMI). [4]

The creation of an updated score could provide a new basis for improving the outcomes of these patients.

Despite the fact that the management of patients with ACS has evolved significantly in the last ten years, this condition is classified as a disease with a reserved prognosis, since there are a number of complications that can occur unpredictably and any effort to predict these complications is beneficial.

Recent studies have shown that there is a link between the prognosis of patients with ACS and the intensity of the inflammatory process. [5-7] In addition, there is a wealth of information in the literature indicating that anisocytosis in acute coronary syndrome (expressed by RDW), large

red blood cells (expressed by high MCV), large platelets (expressed by MPV), and platelet size variability (expressed by PDW) are all associated with the prognosis for these patients. [8-10]

New predictive markers can be found in patients with acute myocardial infarction (AMI) by studying the relationship between the extent of the inflammatory process and their prognosis. Recent data demonstrate the predictive role of various hematological ratios – including NLR (neutrophils/lymphocytes), PLR (platelets/lymphocytes), MLR (monocytes/lymphocytes) and LMR (lymphocytes/monocytes) – in patients who have suffered an acute myocardial infarction. However, there is still no information in the field of cardiology on how the erythrocyte-lymphocyte/monocyte/neutrophil interaction works and whether it can influence the prognosis of patients. Therefore, a seemingly simple question arises, but complex in terms of the pathophysiological phenomena underlying the answer to this question: is there an interaction between erythrocytes and other cells during acute coronary syndrome? Moreover, can this relationship influence the prognosis of the patient with ACS?

Under these conditions, through the current study I aimed to analyze a series of hematological reports (MRR-monocytes/erythrocytes, LRR-lymphocytes/erythrocytes, NRR-neutrophils/erythrocytes), respectively hematological parameters (MCV, RDW, MPV, PDW) correlated with the prognosis of patients with ACS.

The identification of simple and quick parameters to obtain, from the first minutes of a patient's arrival in the emergency room, would constitute a strong point for tracing the prognosis of these patients, imposing a personalized therapeutic strategy that could prevent an evolution burdened with complications.

If in the field of cardiology, this question has not been researched to date, in oncology, it has been demonstrated that ratios such as MRR (monocytes/erythrocytes), LRR (lymphocytes/erythrocytes), NRR (neutrophils/erythrocytes) are correlated with the prognosis of patients with breast cancer.[13] Thus, in the current medical literature, the only study in which these are cited is the one in oncology. As for the other hematological parameters - MCV, RDW, MPV, PDW, there are studies that have correlated their value with the prognosis of patients with ACS. These correlations find their explanations in the pathophysiology of acute coronary syndrome:

1. The study conducted in 2018 by WU and his collaborators demonstrated a statistically significant association between MCV value and mortality rate in patients with BCI. [8]

2. The study conducted in 2023 by Ying Sun et al. demonstrated that RDW value can predict the phenomenon of no-reflow in patients with STEMI. [9]

3. The research conducted in 2022 by Toshiaki et al highlighted how RDW value, respectively MPV value predict cardiovascular complications and death rate in patients with STEMI. [8-10]

The above-mentioned studies emphasize the predictive role of these markers in patients with ACS. However, there is no single study that includes all these parameters and tries to demonstrate whether these parameters could replace the classic stratification scores in patients with acute myocardial infarction.

Why is risk stratification necessary in patients with ACS?

In 2023, the European Society of Cardiology published the new ACS guideline, updating the pre-existing chapters with new information such as the timing of invasive management in NSTEMI, the pretreatment strategy, the strategies for multivessel ischemic coronary disease, but also the need for imaging in management (coronary CT angiography, MRI) and intracoronary imaging investigations - optimal coherence tomography (OCT) and intravascular ultrasound (IVUS).

According to the new guideline, in patients with NSTEMI, an immediate invasive strategy (<2 hours) is preferred in those at very high risk (recurrent-refractory chest pain, hemodynamic instability, cardiogenic shock, mechanical complications, life-threatening arrhythmias, ECG changes in dynamics).

An early strategy (within the first 24 hours) is recommended if the patient has at least one of the criteria for high-risk NSTEMI (NSTEMI diagnosis confirmed according to the current algorithm, Grace score >140 points, changes in the dynamics of the ST segment/T wave, transient ST segment elevation). [11] There are studies that have compared the immediate invasive strategy, compared to coronary angiography performed beyond 24 hours.

The RIDDLE NSTEMI trial (Randomized Study of Immediate vs. Delayed Invasive Intervention in Patients with NSTEMI) demonstrated that patients who benefited from early revascularization (<2 hours) had a lower mortality and reinfarction rate at 30 days compared to those who underwent revascularization later (2-72 hours). [12]

The same result was demonstrated by the EARLY Trial (Early or Delayed Revascularization for Intermediate and High-Risk Non-ST-elevation Acute Coronary Syndrome), highlighting better results regarding recurrent ischemic events in patients who benefited from immediate invasive revascularization (<2 hours) versus late invasive revascularization (12-72 hours). [13]

Except for very high risk and high-risk patients, early revascularization did not improve the final outcomes compared to the late strategy, data presented in the VERDICT trial (Very Early Versus Deffered Invasive Evaluation Using Computerized Tomography). [13]

In the risk stratification in these patients, the GRACE and TIMI scores constitute an important pillar, but the creation of an updated score could constitute a new foundation for improving outcomes in these patients.

THE ORIGINAL PART

Working hypothesis and general objectives

Given the information presented above, we established the following working hypotheses:

1. The MRR (monocyte/erythrocyte), NRR (neutrophil/erythrocyte), LRR (lymphocyte/erythrocyte) ratios correlate with the prognosis of patients with acute myocardial infarction

2. The hematological parameters MCV, RDW, MPV, PDW correlate with the prognosis of patients with acute myocardial infarction and can replace the GRACE score in NSTEMI patients, guiding the timing of the invasive strategy

The main objective of the study is to test the working hypothesis according to which the MRR, NRR, LRR ratios can constitute new predictive factors in patients with acute myocardial infarction.

The secondary objective is to demonstrate the correlation between hematological parameters (MCV, RDW, MPV, PDW) and the prognosis of patients with acute myocardial infarction, respectively demonstrating a possible correlation between these parameters and the GRACE score.

General research methodology

In order to test these hypotheses, we conducted a prospective observational study, conducted in the Cardiology Clinic of the Bagdasar-Arseni Emergency Clinical Hospital. Data were collected between January 2022-April 2023.

The diagnoses of STEMI and NSTEMI followed the indications of the latest ESC guidelines for acute coronary syndromes.

Patients with a pathology that could have interfered with the number of neutrophils, lymphocytes, monocytes, erythrocytes (inflammatory diseases, collagenoses, vascular diseases, autoimmune diseases, neoplastic diseases, acute or chronic infectious diseases, severe liver and/or kidney diseases, hematological disorders, moderate-severe anemia, moderate-severe

thrombocytopenia, recent hemorrhage, radiotherapy/chemotherapy in the last 30 days, acute stroke, PE or DVT) were excluded. Of the 316 patients hospitalized with the diagnosis of acute myocardial infarction, following the application of the exclusion criteria, 261 remained eligible (163 patients hospitalized with the diagnosis of STEMI and 98 with the diagnosis of NSTEMI).

Demographic data (age, ethnicity, sex), anthropometric measurements (BMI-body mass index), medical history (old myocardial infarction or other disease that could interfere with our results – see exclusion criteria above), additional cardiovascular comorbidities (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity) were collected.

Laboratory data (complete blood count, MCV, RDW, MPV, PDW, NT-proBNP, high-sensitive troponin at admission and its peak value, myocardial necrosis enzymes at admission and their peak value, creatinine, AST, ALT, LDH) were analyzed.

The NRR ratio was defined as the absolute neutrophil count divided by the absolute red blood cell count, the MRR was calculated by dividing the absolute monocyte count by the absolute red blood cell count, and the LRR was obtained by dividing the absolute lymphocyte count by the absolute red blood cell count.

LVEF (Left Ventricular Ejection Fraction) values were obtained by transthoracic echocardiography performed during hospitalization. The modified biplane Simpson method was used to calculate left ventricular end-diastolic volumes (LVEDVs) and end-systolic volumes (LVESVs) of 4 and 2 chambers, respectively.

The decision to perform surgical revascularization was based primarily on the characteristics of the angiographic lesion. Factors such as location, size, and complexity of the lesion had a critical impact on determining the need for surgery. It is noteworthy that this decision was individualized and involved the contribution of a multidisciplinary team of healthcare professionals, including cardiologists and cardiac surgeons.

Statistical results were obtained using logistic and linear regression models. Box plots, histograms, distribution representations and ROC curves were used. Data modeling was performed using the python programming language, together with classic modeling packages such as panda, numpy, statmodels.

Regarding the statistical significance of the regression model, a p-value threshold of 0.05 was used to determine whether the model was statistically significant. Based on the analysis of the

regression model, we obtained a mathematical formula represented by the following model: Score for Event Y = β_0+β_1 X.

Where X is the potential predictor used to check whether it is likely to be a real predictor. Having estimated beta 0 and beta 1, we were able to calculate the score. In order to obtain more interpretability from this model and the obtained score, we converted the score to probability. For this, we used the following classical relationship between score and probability from logistic regression theory: Probability = 1/(1+e^(-score)).

To analyze the cut-off value of MCV, RDW, MPV and PDW in estimating Killip class III-IV, we used the ROC curve.

The research included 3 studies, the first including 98 patients with NSTEMI, in which the predictive role of the NRR, MRR, LRR ratios was analyzed. The second study included 163 patients diagnosed with STEMI and pursued the same objective - demonstrating a possible predictive value of the NRR, MRR, LRR ratios in these patients.

The third study followed the correlations between MCV, RDW, MPV, PDW and the prognosis of patients with NSTEMI (patients included in the first study).

Study 1- Predictive role of NRR, MRR, LRR in patients with NSTEMI (Chapter 6)

Study 1 included a group of 98 patients diagnosed with NSTEMI, who were evaluated in terms of NRR, MRR, LRR reports.

The objectives of our study were established as the presence of Killip class III/IV, LV systolic function, recommendation for surgical revascularization, in-hospital mortality, 30-day mortality, 30-day readmission, acute kidney injury.

The statistical results of the first study revealed the following findings:

• The NRR report is statistically correlated with the extent of myocardial injury, with left ventricular systolic dysfunction, severe post-AMI heart failure (Killip class III-IV- cut off value =0.00436). In addition, the NRR value is directly proportional to the presence of severe coronary lesions requiring surgical revascularization, with a cut-off value of 0.00363. There were no statistically significant associations between NRR and in-hospital mortality or 30-day mortality.

• Regarding the LRR ratio, its increased value predicts Killip class III/IV (cut-off of 0.00203), in-hospital mortality (cut-off of 0.00477), but does not predict 30-day mortality, LVEF value, NT-proBNP, or the presence of renal dysfunction.

• Regarding the MRR ratio, it has a value directly proportional to NT-proBNP, predicts severe post-AMI heart failure (Killip class III/IV), renal dysfunction, and is associated with the need for cardiac surgery (cut-off of 0.000329).

The results of this study were published in the journal Healthcare. [14]

Study 2- Predictive role of NRR, MRR, LRR ratios in patients with STEMI (Chapter 7)

The LRR ratio was shown to be an independent predictive marker for the use of inotropic and vasopressor support (cut off value = 0.0031), Killip class III-IV (cut off value = 0.0051), in-hospital mortality (cut off value = 0.0047), renal injury in acute myocardial infarction, but was not associated with myocardial parietal stress. In addition, this ratio was directly proportionally correlated with the TIMI score, but not with the HEART or GRACE scores.

Our suggested predictive marker shows correlations with post-acute myocardial infarction heart failure and renal injury, outcomes that are part of the GRACE score. The LRR ratio not only predicts in-hospital mortality, but also predicts the likelihood of requiring inotropic and vasopressor support, and the extent of myocardial injury - all of which are not covered by the GRACE or HEART score. Thus, this predictive marker that we propose highlights the underlying pathophysiological processes during ACS, going beyond what the GRACE and HEART score imply (clinical and biological picture). This could explain the lack of correlation between LRR and the GRACE and HEART scores. Larger studies with multicenter patient cohorts are needed to confirm or refute this lack of correlation, given the relatively small sample size in our study.

Our findings highlight the immense potential of this simple algorithm to provide a crucial short-term risk assessment for STEMI patients, even before revascularization.

LRR emerges as a cost-effective, reliable, and readily available inflammatory biomarker with significant implications for risk stratification in STEMI patients, providing clinicians with

an invaluable tool to improve outcome predictions and mitigate adverse events in high-risk cohorts.

Regarding the NRR and MRR ratios, they were correlated with the need for positive inotropic and vasopressor support, respectively the extent of myocardial injury (represented by the hscTnI peak), in addition, MRR being directly proportionally correlated with the TIMI score.

The results of this study were published in the journal Healthcare. [15]

Study 3- Predictive role of MCV, RDW, MPV, PDW in patients with NSTEMI (Chapter 8)

In this study, we demonstrated a statistically positive correlation between MCV and Killip class III-IV (cut off value =104 fl), respectively in-hospital mortality (cut off value =108 fl). Regarding the degree of myocardial parietal stress after acute myocardial infarction, we highlighted a statistically relevant linear relationship between NT-proBNP and RDW value, respectively a tendency for NT-proBNP to increase as the RDW value increases.

In addition, RDW was associated with renal dysfunction, length of hospital stay, likelihood of referral for cardiac surgery, and diagnosis of trivessel coronary artery disease.

In multivariate logistic regression analysis, there was a statistically significant positive correlation between PDW and 30-day mortality, with a cutoff value of > 19%.

The most likely pathophysiological mechanism involved in this relationship is represented by the pro-inflammatory status and high oxidative stress in ACS, which lead to a release of immature, larger erythrocytes with a reduced lifespan, leading to anisocytosis, hence higher MCV and RDW values in these patients. When red blood cells enter an area of ischemia and high oxidative stress, a series of structural changes occur in them (rearrangement of the cytoskeleton, loss of asymmetry of lipid layers). In addition to mechanical changes (loss of deformability), intracellular accumulation of oxidative products occurs, such as lipid oxidation products, 4-hydroxynonenal, which further maintain the inflammatory process. At the same time, these structural and mechanical changes in macrocytic erythrocytes lead to a reduction in the antioxidant capacity of the erythrocyte system, which affects oxygen transport to the myocardium.

Analyzing the data collected from our patient cohort, we concluded that the cutoff value for PDW to predict 30-day mortality was 19%, while the cutoff value for MPV to predict Killip class III-IV in patients with NSTEMI was 11.7 fl.

The explanations for why high MPV and PDW values are associated with a poor prognosis are found in the pathophysiological processes within ACS. During acute myocardial infarction, due to increased oxidative stress, large platelets are released into the circulation, which are much more metabolically active, with a higher prothrombotic material and with the release of proinflammatory cytokines.

However, we could not show a correlation between the GRACE score and MCV/MPV/PDW/RDW. This is because the predictive markers we proposed serve as surrogate indicators of the pathophysiological processes (including oxidative stress and increased proinflammatory status) that occur during acute coronary syndrome, going beyond the clinical and biological aspects captured by the GRACE score. These observations may elucidate the absence of a correlation between these markers and the aforementioned score. Finally, it is essential that studies involving larger, multicenter cohorts of patients be performed either to confirm the lack of correlation or, conversely, to establish whether the relatively small cohort of patients in our study influenced this result.

The results of this study were published in the journal Applied Sciences. [15]

Study Limitations

In our study, we encountered several limitations. First, we evaluated the proposed ratios as predictive markers only at admission, but without further evaluation of them during the hospitalization. An optimal strategy would involve measuring these parameters at different stages and performing comparative investigations. In addition, this study was limited to a single center with a relatively limited cohort of patients, highlighting the need for future large-scale studies. Furthermore, we were unable to follow the long-term prognosis of these individuals, which may limit the predictive value of these ratios for long-term risk.

Conclusions

The final conclusions that emerge from the studies presented above highlight the prognostic importance of the NRR, LRR, MRR ratios, but also of the hematological parameters (MCV, RDW, MPV, PDW) in the population of patients with NSTEMI and are presented in detail below:

• NRR is correlated with the extent of myocardial injury

• NRR is correlated with severe post-acute myocardial infarction heart failure (Killip class III-IV), and with the help of the ROC curve we established the cut off value of 0.00436, beyond which the risk of being in Killip class III-IV increases directly proportionally

• NRR is associated with severe coronary lesions that require surgical revascularization, and through the ROC curve we established a threshold value beyond which the probability of needing cardiac surgery increases proportionally (0.00363)

• NRR is inversely proportional to LVEF, so that the higher this ratio is, the higher the probability that the function LV systolic function to be more severely affected

• NRR was not statistically associated with in-hospital mortality or 30-day mortality

• Regarding the LRR ratio, using a linear model, we found a statistical association between this ratio and in-hospital mortality, respectively a trend of increasing the risk of death of patients with NSTEMI as the LRR value increases. The cut-off value for the risk of death based on the LRR value was 0.00477

• LRR is associated with an increased risk of developing Killip class III/IV, having a cut-off value of 0.00203

• LRR was not correlated with 30-day mortality, LVEF, NT proBNP, renal dysfunction

• MRR statistically correlated with NT-proBNP value

• Regarding the recommendation for cardiac surgery, we found that patients with a higher MRR ratio (i.e. above the cut-off value of 0.000329) have a higher probability of receiving this recommendation.

• MRR predicts severe post-AMI heart failure (Killip class III/IV), with a cut-off value of 0.000402

• Our study revealed that a higher MRR ratio was associated with a higher risk of renal dysfunction

• In multivariate logistic regression analysis, there was a statistically positive correlation between MCV and Killip class III-IV, respectively in-hospital mortality. Using a cut-off value of > 104 fl for MCV, we can identify patients with NSTEMI who have a very high risk of developing Killip class III-IV, while a cut-off value of > 108 fl was suggestive of in-hospital mortality

• Regarding the degree of myocardial parietal stress after acute myocardial infarction, we highlighted a statistically relevant linear relationship between NT-proBNP and RDW value, respectively a trend of increasing NT-proBNP as the RDW value grows.

• In addition, using the same linear regression model, we found a linear relationship between RDW and renal dysfunction, respectively a directly proportional relationship

• We demonstrated a statistically significant link between the length of hospitalization and the RDW value

• Furthermore, an RDW value of > 16% is correlated with an increased probability of cardiac surgery recommendation

• An RDW value of > 17% is associated with the diagnosis of trivascular coronary artery disease

• In the multivariate logistic regression analysis, there was a statistically positive correlation between PDW and 30-day mortality, the cutoff value being > 19%

• Using a cutoff value of > 11.7 fl for MPV, we can identify NSTEMI patients who have a very high risk of developing Killip class III-IV

Regarding the group of patients with STEMI, our study outlined the following conclusions:

1) LRR proved to be an independent predictive marker for the use of support inotrope and vasopressor (cut off value = 0.0031)

2) LRR predicts severe post-acute myocardial infarction heart failure (Killip class III-IV), and using the ROC curve, we established a cut off value of 0.0051, beyond which the risk of being in Killip class III-IV increases directly proportionally

3) Regarding renal injury, we found a statistically relevant association between this variable and the LRR value, namely that there is a tendency for renal dysfunction to increase as the LRR value increases

4) LRR was not associated with myocardial parietal stress (no statistically significant relationship was established with the NTpro-BNP value)

5) Regarding in-hospital mortality, we demonstrated a statistical association between this variable and LRR, namely that there is a tendency for the risk of in-hospital death of patients with STEMI to increase as the LRR value increases. The cut-off value for the risk of death based on the LRR value was 0.00477

6) LRR is correlated with the extent of myocardial injury

7) LRR is directly proportionally correlated with the TIMI score, but not with the HEART or GRACE scores

8) The NRR and MRR ratios predict the need for positive inotropic and vasopressor support, respectively, the extent of myocardial injury (represented by the hscTnI peak), in addition, the MRR is directly proportionally correlated with the TIMI score.

Personal contributions

The current study represents the first study that attempted to demonstrate the predictive role of the MRR (monocyte/erythrocyte), NRR (neutrophil/erythrocyte) and LRR (lymphocyte/erythrocyte) ratios in patients with acute myocardial infarction with ST-segment elevation, respectively in patients with acute myocardial infarction without ST-segment elevation. According to the information previously presented, these ratios demonstrated an important predictive value regarding the complications of acute myocardial infarction.

The secondary objective of the study was to demonstrate the hypothesis that hematological parameters such as MCV, RDW, MPV and PDW correlate with the prognosis of patients with acute myocardial infarction without ST-segment elevation and can complement or replace the GRACE score in patients with NSTEMI, thus influencing the timing of invasive intervention.

As previously mentioned, there are numerous statistically significant correlations of these reports with the prognosis of patients with acute myocardial infarction. In addition, our study established through ROC curves cut-off values beyond which the risk of the respective complication increases proportionally.

However, we could not show a correlation between the GRACE score and MCV/MPV/PDW/RDW. This is because the predictive markers we proposed serve as surrogate indicators of the pathophysiological processes (including oxidative stress and increased proinflammatory status) that occur during acute coronary syndrome, going beyond the clinical and biological aspects covered by the GRACE score. These observations may elucidate the absence of a correlation between these markers and the aforementioned score.

Finally, it is essential that studies involving larger, multicenter cohorts of patients be conducted to either confirm the lack of correlation or, conversely, to establish whether the relatively small cohort of patients in our study influenced this result.

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1. **Jercălău CE**, Andrei CL, Brezeanu LN, Darabont RO, Guberna S, Postolea G, Ceban O, **Sinescu CJ**, Unveiling the Hidden Potential of Simple but Promising Blood Cell Parameters on Acute Myocardial Infarction Prognostication. *Applied Sciences*. 2024;14(6):2545. doi:10.3390/app14062545, FI 2.5/2024, https://www.mdpi.com/2718022

2. **Jercălău CE**, Andrei CL, Brezeanu LN, Darabont RO , Guberna S, Catană A, Lungu MD, Ceban O, **Sinescu CJ**, Lymphocyte-to-Red Blood Cell Ratio-The Guide Star of Acute Coronary Syndrome Prognosis, *Healthcare*.2024;12(12):1205.doi:10.3390/healthcare 121121205, FI 2.4/2024, https://www.mdpi.com/2831974,

3.**Jercălău CE**, Andrei CL, Darabont RO, Guberna S, Staicu AM, Rusu CT, Ceban O, **Sinescu CJ**, Blood Cell Ratios Unveiled:Predictive Markers of Myocardial Infarction Prognosis. *Healthcare*. 2024;12(8):824. doi:10.3390/healthcare12080824, FI 2.4/2024, https://www.mdpi.com/2750448