PLATELET DYNAMICS IN COVID-19: UNRAVELING THE CONNECTION TO ACUTE MYOCARDIAL INFARCTION

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PLATELET DYNAMICS IN COVID-19: UNRAVELING THE CONNECTION TO ACUTE MYOCARDIAL INFARCTION (Abstract): **Aim**: Inflammation is the body`s physiological defensive feedback occurring in vascularized tissues in response to damaging stimuli. The occurrence of an acute myocardial infarction is the catalyst for a massive spike in inflammatory activity throughout the system. The **aim** was to determine to what extent positive COVID-19 status alters the extent of this inflammatory response. **Materials and methods:** We retrospectively analyzed clinical and biochemical data from 54 patients with confirmed acute coronary syndrome, equally distributed for COVID-19 infection status prior to admission. Demographic parameters were mostly uniform in our study population. **Results:** Circulating cardiac injury markers returned a not statistically significant tendency towards higher values in COVID-19 infected subjects. Inflammation markers wise, C-reactive protein and white blood cell count were significantly higher in COVID-infected group ($p < 0.05$). Novel inflammatory indexes Neutrophil-and Monocyte- to HDL ratio depicted a statistically significant upward trend towards the infected individuals. Distinctly, the Neutrophil-to-Lymphocyte ratio was similar across the study population (independent 2-tailed t-test $p = 0.287$). Systemic immune-inflammation index (SII) returned an inverse trend compared to NHR and MHR, with statistically significant lower values for COVID-19 infected patients. SII accurately predicted in-hospital death for the whole population (AUC: 0.733; CI (0.548, 0.917)) and for COVID-19 infected group (AUC: 0.841; CI (0.685,0.998)). **Conclusions:** Platelet count, a component of the composite index SII, exhibited an invariable inverse trend compared to any other inflammation surrogate marker, with lower counts in the infected group regardless of adjustments. Despite the activated endothelial phenotype in the subacute phase of myocardial infarction, a pre-existing positive COVID-19 infection status is strongly associated with low platelet count values and flare-up of the immune system. **Keywords:** INFLAMATORY INDEXES, PLATELET COUNT, ACUTE MYOCARDIAL INFARCTION, COVID-19.

INTRODUCTION

Acute manifestation of ischemic heart disease, ST-elevation acute myocardial infarction (STEMI) is a life-threatening type of acute coronary syndrome (ACS) characterized by extent cardiac muscle damage, resulting in a more severe prognosis and a substantially higher mortality rate compared to non-STEMI. Regardless of the myocardial infarction subtype, an early

inflammatory response is triggered by the coronary occlusion.

This sudden burst of inflammation is the perfect illustration of balanced contrast: on one side of the inflammation effects there is the reparative function, but on the other side, damaging pathways constitute the basis for negative outcomes such as increased risk of heart failure, reduced ejection fraction, and ultimately death (1, 2).

Both STEMI and SARS-CoV-2 (COVID-19) infection are pathological entities revolving around inflammation and thrombosis. The severe endothelial damage triggered by the "cytokine storm" in COVID-19 infection is responsible for the disrupted communication between platelets, endothelial cells and leukocytes, laying the premises for recurrent cardiovascular thrombo-embolic events (3). The cellular damage induced by viral replication and local immune response is reflected into a mast cell release of Platelet Activating Factor (PAF), the most potent molecule to elicit platelet activation (4). Furthermore, a unique feature to COVID-19 virus is the Spike protein`s ability to "prime" platelets, leading to faster degranulation and upregulated aggregation activity in response to usual stimuli (collagen, PAF, adenosine diphosphate) (5). In agreement with the increased platelet activity, severe COVID-19 cases consistently demonstrate low platelet counts, although changes in platelet volume indexes are less uniform (6, 7, 8).

There is high interest in finding the optimal inflammation-derived parameter for predicting odds for mortality long after event onset. The neutrophil-HDL ratio (NHR) and the monocyte-HDL ratio (MHR) are some of the indexes used. Patients with acute myocardial infarction, regardless of the affected area, demonstrate significantly higher values for these indices compared to controls (9). Following the onset of the ischemic event, the neutrophil-to-lymphocyte ratio (NLR) proves prognostic value in terms of survival rate and adverse events in patients who have undergone stent-assisted mechanical recanalization (percutaneous coronary intervention - PCI) (10). Likewise, in patients suffering from COVID-19 infection, NHR and MHR rise significantly as a consequence of the sharp increase in the neutrophil fraction typical to severe cases (11). Mirroring the patients suffering a STEMI, NLR yields prognostic value for mortality also in patients with COVID-19 infection at admission (12). The simultaneous presence of the two conditions (i.e. viral infection and cardiovascular event) may alter the previously noted predictive behavior.

We first examined the mean values of selected novel blood cell count-derived indexes between two groups of patients with STEMI, the key difference between groups represented by COVID-19 infection status. Furthermore, considering the essential role of platelets in the pathophysiology of both COVID-19 infection and myocardial infarction sequence, we assessed the interaction between the two conditions by studying platelet count at admission. Ultimately, this retrospective study checked the influence of pre-existing COVID-19 infection upon the distribution of the aforementioned parameters in patients found in the acute phase of STEMI.

MATERIALS AND METHODS

Study design. This study retrospectively examined patients who presented to the Emergency Department of the Institute of Cardiovascular Diseases Iasi and were

diagnosed with acute myocardial infarction in an angiography intervention setting - procedure which met simultaneously diagnostic and treatment steps. Percutaneous coronary angiography was performed on all patients included in the study

Timeframe. This study focused on the period of time between 1st of June and 1st of July 2020. This time interval was considered as the first peak in the number of detected cases of acute COVID-19 infection in Romania.

Diagnostic procedure. Initial diagnosis of myocardial infarction was suspected during the ambulance phase of the "chain of survival", by corroborating the patient`s symptom report, level of Troponin I, and the aspect of electrocardiogram. All included individuals are in the acute phase of myocardial infarction. Patients with history of previous percutaneous interventions, or myocardial infarction diagnosed by a medical specialist have been excluded. Collection of samples and testing for COVID-19 infection was done immediately upon admission by earliest real-time Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) tests approved by the European Union regulation body.

Outcomes. Data was extracted from computerized and paper-based records in the hospital archive. Collected variables included demographic information, blood laboratory work, medical history and in-hospital mortality. The sampling of the biological fluids and situses needed for the presented data was performed in the time window between ambulance retrieval of the patient and first 60 minutes upon hospital arrival, before percutaneous intervention has been attempted. The primary outcome is Platelet Count. Other outcomes of interest revolve around the inflammatory status amplitude. We have not limited to the traditional markers concerning systemic inflammation (Fibrinogen, C-reactive protein), but we have also included newer parameters as emerging indicators of vascular health: Neutrophil - to - Lymphocyte, Neutrophil - to -HDL, Monocyte-to-HDL ratios (MHR).

Statistical analysis

Descriptive statistics include absolute numbers, percentages, mean, standard deviation (SD), median, and interquartile range, in accordance with the variable type and distribution symmetry. Patients were categorized based on the status of COVID-19 infection at admission. Categorical variables were analyzed using the Chi-square test. The normality of distribution for continuous variables was visually assessed using Q-Q plots and the Shapiro-Wilk test. Qualitative data was compared using Chi-Square test. Independent quantitative data were compared using the two-tailed two-sample Student`s t-test and the Mann-Whitney U-test, where appropriate. Low-count samples were compared by bootstrapping. Correlation between monotone continuous variables was assessed using Pearson's test. A two-tailed p value <0.05 was convened for statistically significant difference. Adjustment for confounders in the data analysis phase was performed by stratification. Where simple models were proposed, the goodness of fit (accuracy of model) was tested by using the Area Under the Curve (AUC) for ROC (Receiver Operating Characteristic) and the Confidence Interval (CI). Cutoff value for best accuracy was assessed using Youden index. Data

analysis was carried out using the IBM *SPSS Statistics for Windows, version 26* (SPSS Inc., Chicago, IL).

Ethical approval

Upon admission, all patients gave their informed consent allowing limited post-hoc use of their clinical and laboratory data, in agreement with Declaration of Helsinki and local ethical regulations. Ethical approval was received from Grigore T. Popa University of Medicine and Pharmacy in Iasi, Romania, the Scientific Research Committee (161/07.03.2022). The retrospective design waived any further need for informed consent from the patients involved in this study.

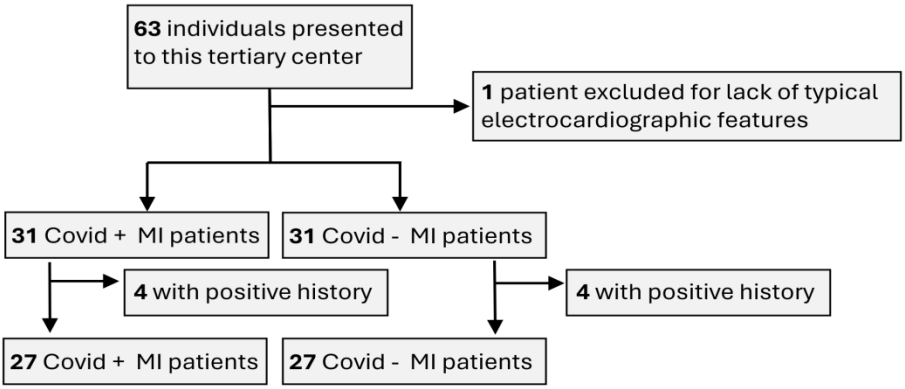


Fig. 1. Flowchart depiction enrollment in our study. 1 patient presented with neither ST-elevation nor abnormal rhythm. Unfavorable cardiovascular history refers to previous percutaneous interventions or myocardial infarctions.

We included 54 patients in our study, as depicted in first figure, equally distributed in the two arms (COVID-19 positive or infected, and COVID-19 negative or controls). Between-groups comparison of variables yielded no statistically significant difference, with the exception of diabetes mellitus (higher in the infected group) (tab. I).

A Chi-square test of independence showed that there was no significant association between renal function assessed by estimated glomerular filtration rate and COVID-19 infection status in this sample, X^2 (df = 2, N = 52) = 0.33, p = 0.85. The laboratory work-up, described in second table, was focused on the main components of blood cell count, traditional inflammatory markers, traditional cardiac injury markers and typical lipid metabolism indicators including cholesterol fractions, later part of the more intricate indicators of systemic inflammatory status. We notice a statistically and clinically significant difference regarding white blood cell count in favor of the infected group. Consequently, the absolute count of polymorphonuclears and lymphocytes are also significantly different ($p < 0.05$), but not their relative percentages. This trend does not extend to monocyte count, albeit there is a small gap to the statistical significance cut-off value. Platelet count exhibits a statistically significant drop in COVID-19 infected patients ($p = 2 \times 10^{-4}$). Conversely, there is no difference between the fractions of neutrophils, lymphocytes or monocytes with respect to COVID-19 status.

TABLE I.

General characteristics of the population included in the study, divided by COVID-19 status at admission.

Variable	COVID-19 + (infected) N = 27	COVID-19 - (controls) N = 27	p
Demographics			
Age, years (Mean ± SD)	**66.7 (11.4)**	**62.5 (9.5)**	0.15
Female sex	**5 (18.5)**	**6 (22.2)**	0.73
Comorbidities			
Hypertension	**16 (59.3)**	**16 (59.3)**	1
Dyslipidemia	**8 (29.6)**	**7 (25.9)**	0.77
Diabetes mellitus	**13 (48.1)**	**6 (22.2)**	**< 0.05**
Smoking	**7 (25.9)**	**9 (33.3)**	0.55
Alcohol abuse	**9 (33.3)**	**9 (33.3)**	1
Kidney function (eGFR)			
Normal renal function	**11 (40.7)**	**10 (37.0)**	0.78
Mild impairment (G2)	**11 (40.7)**	**14 (51.9)**	0.41
Moderate impairment (G3a)	**3 (11.1)**	**3 (11.1)**	1
Moderate impairment (G3b)	**1 (3.7)**	**0 (0)**	*N/A*
Severe impairment (G4)	**1 (3.7)**	**0 (0)**	*N/A*
Chronic treatment			
ACEI	**5 (18.5)**	**11 (40.7)**	0.07
Statins	**5 (18.5)**	**8 (29.6)**	0.34
Antiplatelet	**2 (7.4)**	**6 (22.2)**	0.13

ACEI, Angiotensin converting enzyme inhibitors. Chronic Kidney Disease stages (G2 – G4) in agreement with current KDIGO guidelines. All values are stated as absolute count and percentage, except otherwise stated.

TABLE II.

Lab investigations compared between the two groups.

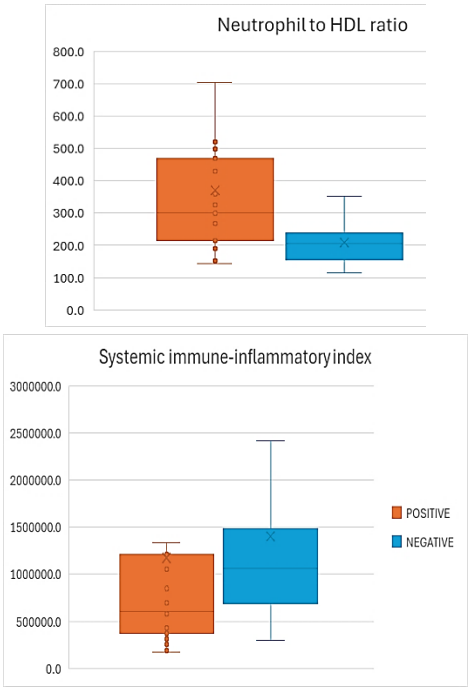
Variable	COVID-19 + (infected) N = 27	COVID-19 – (controls) N = 27	p value
Blood sample parameters			
Hemoglobin, g/dl (Mean ± SD)	13.51 (2.89)	14.48 (1.78)	NS
Anemia (N, %)	11 (40.7)	6 (22.2)	NS
White cells, N/mm^3 (Median, Q_1, Q_3)	16490 (13070, 17930)	12530 (10810, 13480)	***< 0.01***
PMNs, % of WBCs (Median, Q_1, Q_3)	68.6 (65.6, 78.0)	71.3 (66.5, 78.5)	NS
PMNs, N/mm^3 (Mean ± SD)	11732 (3931)	9053 (2482)	***< 0.01***
LYs, % of WBCs (Mean ± SD)	17.3 (8.9)	16.8 (6.6)	NS
LYs, N/mm^3 (Mean ± SD)	2779 (1429)	2058 (776)	***< 0.05***
MOs, % of WBCs (Median, Q_1, Q_3)	9.8 (7.9, 12.7)	9.6 (6.0, 13.0)	NS
MOs, N/mm^3 (Median, Q_1, Q_3)	1385 (1094, 2069)	1075 (767, 1578)	NS
Platelets, N*10^3/mm^3 (Median, Q_1, Q_3)	150 (114, 188)	244 (199, 291)	***< 0.01***

Variable	COVID-19 + (infected) N = 27	COVID-19 – (controls) N = 27	p value
Lipid metabolism			
HDL-Col, mg/dl (Median, Q_1, Q_3)	39 (28.5, 45)	45 (36.5, 49)	***< 0.05***
LDL-Col, mg/dl (Median, Q_1, Q_3)	107.0 (79.0, 138.5)	112.0 (91.1, 159.5)	NS
Total Cholesterol, mg/dl (Mean ± SD)	168.7 (57.8)	201.0 (59.3)	***< 0.05***
Triglycerides, mg/dl (Mean ± SD)	140 (104, 160)	133 (92.5, 191)	NS
Tissue injury/inflammation markers			
C-reactive protein, mg/l (Median, Q_1, Q_3)	62.0 (25, 154.0)	19.9 (6.9, 51.7)	***< 0.05***
Fibrinogen, mg/dl (Median, Q_1, Q_3)	608 (458, 796)	491 (441, 607)	NS
LDH, U/l (Median, Q_1, Q_3)	707 (518, 1122)	587 (467, 798)	NS
CK-MB, U/l (Median, Q_1, Q_3)	153 (108, 352)	105 (81, 192)	NS
TnI, U/l (Median, Q_1, Q_3)	8543 (1405, 9870)	1854 (371, 2821)	NS

PMNs, polymorphonuclear cells; LYs, lymphocytes; MOs, monocytes; HDL, high-density fraction; LDL, low-density fraction of cholesterol; LDH, lactate dehydrogenase; CK-MB, myocardial specific creatinkinase isoenzyme; TnI, Troponin isoform I. Anemia cut-off values according to American Society of Hematology.

Concerning lipid metabolism, there is a statistically relevant difference in HDL-Col values and total cholesterol values, but in opposing directions. While higher HDL-Col in COVID-19 patients is beneficial in terms of atherosclerotic plaque stabilization, higher total Cholesterol is detrimental to vascular wall reactivity. All inflammatory markers depict a slight tendency towards higher values in favor of the COVID-19 infected group, but only C-reactive protein attained statistical significance. Calculation of NLR, NHR and MHR by employing the best test in accordance with their proximity to a normal distribution led to a statistically significant difference in favor of the COVID-19 group limited to NHR ($p = 1.3*10^{-4}$) and MHR ($p = 2.7*10^{-3}$). NLR values were very similar between groups, the slightly higher mean and SD in COVID-19 positive side likely arising from outliers (6.39 ± 5.88 vs 4.95 ± 2.97). In both groups, 67% of values of NLR were outside the normal range. Similar evaluation for SII using the standard formula returned an inverse trend, with lower values in control individuals ($p = 2.7*10^{-2}$). Considering the lack of relevant difference between groups for neutrophils and lymphocytes relative percentage of white blood cells, the only component to account for the difference of means for SII was platelet count. SII and platelet count ($p = 1.6*10^{-4}$) show a statistically significant similar trend towards lower values in positive COVID-19 status patients for the whole sample. These trends are depicted in second figure.

For NHR and MHR adjusting for sex did not cancel the statistical significance in any of the two indices. Adjusting for presence of diabetes mellitus and chronic cardiovascular medication via stratification revoked the statistical significance in NHR. Robustness of NHR was demonstrated by the lack of association with other chronic conditions, age or gender. MHR was sensitive to adjusting for any of the aforementioned factors. The similarities in the formulas for these parameters translates to a strong positive correlation in both the COVID-19 infected group (Pearson $r = 0.84$, $p < 0.001$), and in the entire population (Pearson $r = 0.78$, $p < 0.001$). The control group returned a negative r value ($r = -0.34$, $p = 0.102$) for regression between NHR and MHR, without statistical significance.



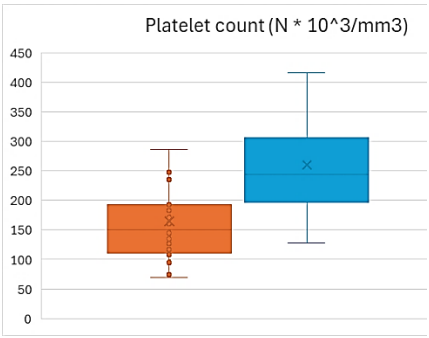


Fig. 2a, b, c. Boxplots for NHR (left), NHR (middle), and SII (right), difference of means are statistically significant ($p < 0.05$). Distribution of MHR closely resembles figure 2a.

Platelet count demonstrated a considerable difference between groups, higher values consistently found in the healthy group. Remarkably, this tendency was opposite compared to the one exhibited by NHR and MHR. The statistical significance is retained after adjustment for anemia, smoking status, and presence of comorbidities (diabetes mellitus, hypertension, alcohol abuse). Adjustment for sex and age by stratification also preserves the statistical significance in platelet count distribution. Adjustment for chronic cardiovascular medication (performed for drugs which impact platelet function – statins, ACEI, and antiplatelet therapy) preserved the statistical significance. Lastly, separate adjustments for renal function revoked the statistical power of platelet count distribution; the myocardial infarction patients with normal renal function as assessed at hospital admission was the only category of patients where the mean difference still held significance.

In this study, COVID-19 status was an accurate predictor for in-hospital death, as highlighted by an Odds Ratio of 15.7 in favor of infected patients. We tested the degree of fit for two hypotheses: a. COVID-19 positive status; b. in-hospital death as simple functions separately for all mentioned composite indexes (NHR, MHR, SII) and for platelet count. All indexes accurately predicted presence of COVID-19 infection, but with lower values of platelet count and SII associated with positive status (tab. III). We then evaluated inpatient death for the whole sample, and separately for the COVID-19 infected individuals. Analysis could not be performed in the control lot since no event occurred. On a whole sample scale, all parameters but platelet count accurately predicted the outcome. Performing the same calculation for

only the infected group canceled prognostic accuracy for MHR also. Platelet count did not return diagnostic accuracy for in-hospital death in any of the attempts.

Despite relying on platelet count, SII maintained prognostic accuracy.

TABLE III.

Area-Under the Curve summary description for three diagnostic accuracy hypothesis tests for the four mentioned prognostic indexes: Neutrophil-to-HDL ratio; Monocyte-to-HDL ratio, Platelet Count and Systemic immune-inflammatory index. N/A, not attempted since the curve was not statistically significant for accuracy test

Hypothesis/index		NHR	MHR	PLC	SII
COVID-19 positive status	AUC, CI	0.768 (0.641; 0.895)	0.711 (0.572; 0.849)	0.798 (0.679; 0.918)	0.675 (0.531; 0.819)
	Cutoff value	268.43 (higher than)	35.39 (higher than)	191250 (lower than)	5.99*10^8 (lower than)
	Youden index	0.519	0.444	0.556	0.370
In-patient death for whole sample	AUC	0.920 (0.838; 0.999)	0.747 (0.568; 0.925)	0.642 (0.426; 0.859)	0.733 (0.548; 0.917)
	Cutoff value	302.22 (higher than)	32.75 (higher than)	N/A	1.19*10^8 (lower than)
	Youden index	0.771	0.5	N/A	0.542
In-patient death for COVID-19 +	AUC	0.857 (0.710; 0.999)	0.666 (0.434; 0.900)	0.476 (0.208; 0.745)	0.841 (0.685; 0.997)
	Cutoff value	307.07 (higher than)	N/A	N/A	1.17*10^8 (lower than)
	Youden index	0.619	N/A	N/A	0.691

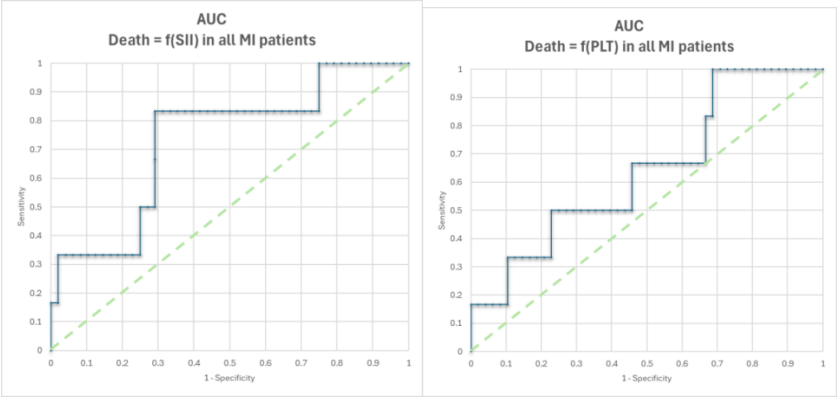


Fig. 3. a, b. Diagnostic test fit for predictors of in-hospital survival. The green interrupted line is the representation of the line of at-random events. MI, myocardial infarction.

Lastly, we checked the independence between relevant chronic medication and inpatient mortality. The Chi-square test for mortality versus ACEI therapy returned a *p* value of 0.044, translating into a potential association between the two categorical variables. Prompted by the previous p value, odds ratio returned a value of OR = 1.21 for mortality in people taking ACEI, but this was not statistically significant. Despite the apparent negative association, the *p* value of 0.83 voided statistical significance.

DISCUSSION

In our study the ratio between the proportions of neutrophils and lymphocytes between groups was not statistically different. However, the absolute white cell count, as well as neutrophil and lymphocyte count showed a statistically significant difference in favor of the COVID-19 infected group. Owing to local protocols at the time of COVID-19 infection wave peak, our study design did not include a third healthy group – i.e. not suffering a major cardiovascular event. Comparing to the expected normal range in recent literature, NLR values in both COVID-19 positive and negative subgroups exceeded the upper limit in 67% of cases (13).

NHR yields good predictive value in COVID-19 patients NLR increase a false indicator due to the early hyperdynamic transitory activity driven by tissular injury in terms of mortality and need for advanced respiratory support (14, 15). MHR demonstrates a similar prognostic predictive potential, although the evidence for this is limited to smaller, less uniform populations (16, 17).

Our study returned a statistically significant difference in favor of the infected study arm for both NHR and MHR. This is likely the result of the higher neutrophil count prompted by the cellular injury, irrespective of the burden generated by the overlapping cardiovascular damage. Monocyte count and MHR values closely mirror the observations noted in NHR. HDL-Col values were not statistically different between groups, discarding the possibility of a high impact of the COVID-19 infection upon lipid metabolism. Both NHR and MHR proved a statistically significant prediction accuracy for in-hospital death by AUC-ROC model curve.

Our results show a statistically significant lower mean value for platelet count in patients infected by COVID-19 ($p < 0.001$). Upon separate adjustment for every baseline feature, the difference between the COVID-19 infected and control groups remained statistically significant in every case, except for renal function.

SARS-CoV-2 interacts with platelets both directly – viral genome inside platelets – and indirectly through the Spike protein. The overactivated platelets amplify the inflammatory cascade through complement activation. An overly enhanced platelet activity is an indicator of damaged self-regulatory ability, the viral loaded platelets being less efficient in controlling viral spread through the body and exhibiting aberrant pro-thrombotic activity (18). The high plasma concentration of platelet-derived granules could indicate a pyroptotic release of platelet-contained vesicles, which in turn is the result of inflammation-driven enhancement of programmed cell death mechanisms (19). All previous mechanisms suggest that with increasing severity of COVID-19 infection there is a proportional decrease in platelet count. Dysregulated thrombosis and coagulation characterizing COVID-19 infection reflect in mild to moderate thrombocytopenia, entity labeled thrombocytopathy by activation (20, 21).

In our research, SII showed accurate

prognostic ability for COVID-19 status, and in-hospital death regardless of infection presence. Notably, and contradicting with existing literature, lower values than cutoff predict the intended event, which likely stems from the involvement of platelet count in the index formula. Since there was not a relevant difference between either neutrophil count or lymphocyte count with respect to COVID-19 infection status, platelet count contributed most to the observed pattern for SII. Robustness of SII was limited, as adjustment for any chronic cardiovascular treatment, chronic comorbid condition, or anthropometric parameter revoked the statistical significance for mean difference between groups. SII was most accurate out of the four parameters when assessing inpatient mortality within the infected subgroup. On the whole sample of myocardial infarction patients, SII was downgraded by NLR for prognostic ability.

In a fundamental approach, RAS axis is comprised of a deleterious component centered on Angiotensin-Converting Enzyme (ACE) and Angiotensin II, and a protective arm implying Angiotensin-Converting Enzyme-2 (ACE-2) and Angiotensin 1-7 (22). At the beginning of the pandemic doubts have risen concerning the safety of continuation of ACE inhibitor (ACEI) therapy, since it would indirectly upregulate expression of ACE-2, the main receptor of COVID-19 (23). Research has since proven that inhibition of RAS axis is beneficial regarding inpatient prognostics, but there is no clear superiority of ACEI drugs versus Angiotensin-Receptor Blockers (24). Hypertensive individuals taking ACEI appear protected against contracting COVID-19 disease and in-hospital events such as intubation and mortality (25, 26). In our study, there is a clinically significant difference in the frequency of encountering ACEI in patients` prescriptions, but it did not attain statistical significance between groups. Testing for association between ACEI medication and in-hospital mortality returned a statistically significant association (Chi-square $p = 0.044$). This link is limited to a simple associative relationship, since odds ratio for mortality as a function of ACEI therapy did not return statistical significance ($p = 0.83$). All in all, albeit an associative tendency between ACEI chronic therapy and survival, the relationship is not statistically significant in this study`s sample of 54 patients.

In our study, the odds ratio for in-hospital mortality was 15.7 for COVID-19 infected group. Similar studies focused on STEMI patients with COVID-19 infection demonstrate a higher mortality in the viral infected group mainly as a result of higher thrombus burden (more extensive thrombosis, or thrombus locations more anatomically challenging) (27). A significant enhancement in inflammatory status may be responsible for the higher odds for severe adverse events in infected patients during the early post-recanalization period (28). Reports concerning overall hospital mortality are inconsistent but generally show a trend for higher odds in COVID-19 infected myocardial infarction individuals (6, 29, 30).

CONCLUSIONS

Immediately following a major acute cardiovascular event (MACE) there is a sudden flare in the inflammation cascade, the backlash of cellular hypoxia and injury. In our study, blood samples have been collected in the early phase of myocardial infarction; consequently, an increased inflammatory status is expected across the whole STEMI population. COVID-19 infection induces a significant systemic inflammatory state independent of the pre-existing

health status. Therefore, COVID-19 positively diagnosed patients would have experienced a higher set point for inflammatory status prior to the onset of the acute cardiovascular event. Most – but not all – markers for extent of inflammatory burden were found to be increased in the COVID-19 positive arm in comparison to the group who did not develop viral infection. In conclusion, under the acute setting of a MACE, pre-existing COVID-19 infection leads to a statistically significant increase in terms of surrogate indexes for extent of systemic inflammation, such as NHR and SII.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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Andreea Clim and Cristian Tudor Cozma contributed equally to this work.

REFERENCES

1. Mueller C, Buettner HJB, Hodgson JM, *et al*. Inflammation and long-term mortality after non-ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. *Circulation* 2002; 105(12): 1415-1415 / doi: 10.1161/01.cir.0000012625.02748.62.
2. Biasucci LM, Liuzzi G, Grillo RL, *et al*. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation* 1999; 99(7): 855-860 / doi: 10.1161/01.cir.99.7.855.
3. Agrati C, Sacchi A, Tartaglia E, *et al*. M. The Role of P-Selectin in COVID-19 Coagulopathy: An Updated Review. *Int J Mol Sci* 2021; 22(15): 7942 / doi: 10.3390/ijms22157942.
4. Klein, M, Dao, V, Khan, F. A Review of Platelet-Activating Factor as a Potential Contributor to Morbidity and Mortality Associated with Severe COVID-19. *CATH* 2021; 27 / doi: 10.1177/1076 0296211051764.
5. Antonopoulou S, Petsini F, Detopoulou M, Theoharides TC, Demopoulos CA. Is there an interplay between the SARS-CoV-2 spike protein and Platelet-Activating factor? *Biofactors* 2022; 48(6): 1271-1283 / doi: 10.1002/biof.1877.
6. Beceren NG, Armağan HH, Oğuzlar FÇ, Cesur E, Gürdal O, Tomruk Ö. Can mean platelet volume be a prognosis predictor in viral infections: An example of COVID-19. *Heliyon* 2023; 9(11): e21983 / doi: 10.1016/j.heliyon. 2023.e21983.
7. Sun H, Liu H, Li J, Kou J, Yang C. Analysis of the Clinical Predictive Value of the Novel Inflammatory Indices SII, SIRI, MHR and NHR in Patients with Acute Myocardial Infarction and Their Extent of Coronary Artery Disease. *J Inflamm Res* 2024; 17: 7325-7338 / doi: 10.2147/JIR.S479253.
8. Pinheiro Machado G, Araujo GN, Carpes CK, *et al* Elevated neutrophil-to-lymphocyte ratio can predict procedural adverse events in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Coron Artery Dis* 2019; 30(1): 20-25 / doi: 10.1097/MCA.0000000000000671.
9. Wang Y, Zhang J, Li H, *et al*. Prognostic Value of Leucocyte to High-Density Lipoprotein-Cholesterol Ratios in COVID-19 Patients and the Diabetes Subgroup. *Frontiers Endocrinol* 2021; 12 / doi: 10.3389/fendo.2021.727419.
10. Colaneri M, Genovese C, Fassio F, *et al*. Prognostic Significance of NLR and PLR in COVID-19: A Multi-Cohort Validation Study. *Infect Dis Ther* 2024; 13(5): 1147-1157 / doi: 10.1007/s40121-024-00967-6.
11. Forget, P, Khalifa, C, Defour, J.P, *et al*. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes* 2017; 10(1): 12 / doi:10.1186/s13104-016-2335-5.
12. Ergenç H, Ergenç, Z, Dog An, M, Usanmaz, M, Gozdas, H.T. C-reactive protein and neutrophil-lymphocyte ratio as pre-dictors of mortality in coronavirus disease 2019. *J Rev Assoc Med Bras (1992)* 2021; 67(10): 1498-1502 / doi: 10.1590/1806-9282.20210679.

13. Argun D, Argun F, Basim P, Bayraktaroglu M. Monocyte-to-High-Density Lipoprotein Cholesterol Ratio: A Candidate Parameter for a Risk Assessment Model in COVID-19. *Clin Lab* 2022; 68: 3 / doi: 10.7754/Clin.Lab.2022.210755.
14. Ergenc H, Ergenc Z, Gozdas HT, Ocak OK, İnce O, Bal T. Monocyte-to-Hdl-Cholesterol Ratio as a Prognostic Marker in COVID-19. *J Pioneer Med Sci* 2025; 13(1): 116-122 / doi: 10.61091/jpms 202413120.
15. Zaid, Y, Puhm, F, Allaeys, I, *et al*. Platelets Can Associate with SARS-Cov-2 RNA and Are Hyperactivated in COVID-19. *Circ Res.* 2020; 127(11): 1404-1418 / doi: 10.1161/CIRCRESAHA 120.317703.
16. Koupenova M, Corkrey HA, Vitseva O, *et al*. SARS-CoV-2 Initiates Programmed Cell Death in Platelets. *Circ Res* 2021; 129(6): 631-646 / doi: 10.1161/CIRCRESAHA.121.319117.
17. Sciaudone, A, Corkrey H, Humphries, F, Koupenova, M. Platelets and SARS-CoV-2 During COVID-19: Immunity, Thrombosis, and Beyond. *Circ Res* 2023; 132(10): 1272-1289 / doi: 10.1161/CIRCRESAHA. 122.321930.
18. Tafazoli A, Anil Kumar, S, Othman M. Thrombocytopathy vs Platelet hyper-reactivity in COVID-19: diverse pathologies, disease outcomes and therapeutic implications. *Platelets* 2022; 33(1): 48-53 / doi: 10.1080/ 09537104.2021.1961718.
19. Maranduca MA, Tanase DM, Cozma CT, *et al* The Impact of Angiotensin-Converting Enzyme-2/Angiotensin 1-7 Axis in Establishing Severe COVID-19 Consequences. *Pharmaceutics* 2022; 14(9): 1906 / doi: 10.3390/pharmaceutics14091906.
20. Onweni CL, Zhang YS, Caulfield T, Hopkins CE, Fairweather L, Freeman WD. ACEI/ARB therapy in COVID-19: the double-edged sword of ACE2 and SARS-CoV-2 viral docking. *Crit Care* 2020; 24(1): 475 / doi:10.1186/s13054-020-03195-9.
21. Hamada S, Suzuki T, Tokuda Y, *et al*. Comparing clinical outcomes of ARB and ACEi in patients hospitalized for acute COVID-19. *Sci Rep* 2023; 13: 11810 / doi: 10.1038/s41598-023-38838-8.
22. Semenzato L, Botton J, Drouin J, *et al*. Antihypertensive Drugs and COVID-19 Risk: A Cohort Study of 2 Million Hypertensive Patients. *Hypertension* 2021; 77(3): 833-842 / doi: 10.1161/HYPER TENSIONAHA.120.16314.
23. Hippisley-Cox J, Young D, Coupland C, *et al*. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020; 106(19): 1503-1511 / doi: 10.1136/heartjnl-2020-317393.
24. Choudry FA, Hamshere SM, Rathod KS, *et al*. High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol* 2020; 76(10): 1168-1176 / doi: 10.1016/j.jacc.2020.07.022.
25. Jabir A, Geevar Z, Mohanan PP, *et al*. COVID-19 infected ST-Elevation myocardial infarction in India (COSTA INDIA). *Indian Heart J* 2023; 75(4): 243-250 / doi: 10.1016/j.ihj.2023.05.009.
26. Goel A, Malik AH, Bandyopadhyay D, *et al*. Impact of COVID-19 on Outcomes of Patients Hospitalized With STEMI: A Nationwide Propensity-matched Analysis. *Curr Probl Cardiol* 2023; 48(4): 101547 / doi: 10.1016/j.cpcardiol.2022.101547.
27. Jiang SQ, Huang QF, Xie WM, Lv C, Quan XQ. The association between severe COVID-19 and low platelet count: evidence from 31 observational studies involving 7613 participants. *Br J Haematol* 2020; 190(1): e29-e33 / doi: 10.1111/bjh.16817.
28. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* 2020; 506: 145-148 / doi: 10.1016/j.cca.2020.03. 022.
29. Bychowski J, Michalski T, Sobiczewski W, Jaguszewski M, Gruchała M. The impact of the COVID-19 pandemic on ST-segment elevation myocardial infarction treatment strategy and outcomes. *Front Cardiovasc Med* 2025; 12: 1522661 / doi: 10.3389/fcvm.2025.1522661.
30. Choi HK, Maity M, Qureshi M, *et al*. Multifaceted Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on ST-Elevation Myocardial Infarction (STEMI): A Literature Review of Incidence, Treatment Modalities, and Outcomes. *Cureus* 2024; 16(3): e57288 / doi: 10.7759/cureus.57288.