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Association of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio with all-cause mortality in patients with ischemia and non-obstructive coronary arteries

Emilian Dumitru Mihai[1,2], Caterina Delcea[1,2*], Adrian Cătălin Buzea[1,2], Gheorghe-Andrei Dan[1,2]

1. Department of Cardiology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
2. Department of Cardiology, Colentina Clinical Hospital, Bucharest, Romania

ABSTRACT

Background: Ischemia with non-obstructive coronary arteries (INOCA) is a frequent coronary syndrome with important impact on morbimortality. Systemic inflammation, a key pathophysiological mechanism in its development, is reflected in diverse biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR). In this retrospective observational study, we aimed to assess the value of NLR, MLR and PLR as predictors of all-cause long-term mortality in INOCA patients.

Methods: Acute/ chronic consecutive INOCA patients hospitalized from January 2014 to December 2019 were included, after excluding pulmonary hypertension, acute non-cardiac pathology, and in-hospital mortality. The primary endpoint was all-cause mortality.

Results: Our cohort included 238 INOCA patients (62.2% female, mean age 64.1±9.5 years). Of all patients, 14.3% reached the endpoint during the mean 5.8±1.1 years of follow-up. Age (OR=1.10, p<0.001), diabetes mellitus (OR 2.54, p=0.01), heart failure (OR=3.73, p=0.003), atrial fibrillation (OR=3.52, p=0.001), severe valve disease (OR=3.99, p=0.001), NT-proBNP (OR=3.28, p<0.001), 3rd tertile NLR (OR=4.33, p<0.001) and 3rd tertile MLR (OR=4.34, p<0.001) were mortality predictors, while the 3rd tertile PLR was not. In multivariable analysis the baseline prediction model included age (HR=1.12, p<0.001) and heart failure (HR=3.78, p<0.001). Adding NLR>2.99 (HR=4.58, p<0.001), MLR>0.36 (HR=4.74, p<0.001), or both increased the power of the predictive model from chi-square 33.00 to 51.08 (p<0.001).

Conclusions: In patients with acute or chronic INOCA, NLR and MLR were independently correlated with all-cause mortality. The most accurate mortality prediction model included NLR>2.99, MLR>0.36, age and the diagnosis of heart failure.

Keywords: INOCA, ischemia with non-obstructive coronary artery disease, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)

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INTRODUCTION

Patients with myocardial ischemia without significant atherosclerotic disease of the epicardial coronary arteries make up a large proportion of those undergoing coronary angiography and represent a challenge in terms of diagnosis, therapy and prognosis [1–3]. Overlooked for a long time, this anginal syndrome has been named ischemia with non-obstructive coronary artery (INOCA) lesions and has been associated with an increased risk of myocardial infarction and heart failure with preserved ejection fraction [4–6]. Low-level chronic inflammation plays an important role in the occurrence of coronary microvascular dysfunction as one of the main pathophysiological mechanisms of INOCA, eventually leading to perivascular inflammation, arterial remodeling and capillary microthrombosis [7,8].

Several immune-inflammatory markers derived from the full blood count and lipid profile like the systemic immune inflammation index (SII), systemic inflammation response index (SIRI) [9], neutrophil-to-lymphocyte ratio (NLR) [10,11], platelet-to-lymphocyte ratio (PLR) [12], neutrophil-to-high density lipoprotein cholesterol (NHR) [13], were proven to be prognostic predictors in obstructive coronary disease [9,13], stroke [10] and heart failure [11,12], as well as in sepsis [14] and neoplasia [15].

* Corresponding author: Caterina Delcea, Department of Cardiology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. E-mail: caterina.delcea@gmail.com

There is limited data about these inflammatory prognostic markers in INOCA patients. Identifying new rapid prognostic markers from the immuno-inflammatory system could be useful for accurate diagnosis, risk stratification and preventing MACE in INOCA patients.

In this study, we aimed to investigate the value of NLR, MLR and PLR as predictors of long-term all-cause mortality in INOCA patients.

METHODS

Study design

Our study investigated consecutive patients admitted for coronary ischemic syndromes and non-obstructive coronary arteries at invasive coronary angiography. This was a cross-sectional, retrospective, observational research.

Study population

Between January 2014 and December 2019, all patients admitted to our department for chronic or acute coronary syndromes, which were confirmed by invasive coronary angiography to have non-obstructive coronary lesions were considered eligible for inclusion.

The inclusion and exclusion criteria, as well as the study methodology were previously described elsewhere [16]. In addition, all patients hospitalized starting from January 2020 were excluded from the initial cohort due to potential interference with SARS-CoV2 infection that could alter the hematological ratios considered in our analysis.

Only patients who gave written informed consent were eligible for inclusion. The study protocol was approved by the hospital's ethics committee, in accordance with the Declaration of Helsinki.

Invasive coronary angiography

All patients underwent invasive coronary angiography (ICA) using Judkins technique with a Siemens Artis Zee angiography system (Siemens Healthineers AG, Munich, Germany). All three main coronary arteries were examined in standard projections to evaluate atherosclerotic narrowing. We excluded any patient with stenosis greater than 50% in any of the three main epicardial coronary arteries. Each coronary angiography was independently evaluated by two operators.

Definitions

Ischemia with no obstructive epicardial coronary arteries was diagnosed in patients with either chronic stable angina with demonstrable ischemia, or in patients with acute coronary syndromes, undergoing coronary angiography without a diagnosis of significant stenosis [1,17].

Hematological parameters

On admission a standard blood sample was obtained for determining blood type, full blood count including a white cell differential, inflammation and biochemistry markers.

Sample processing occurred within a median of 60 minutes from the collection. Complete blood count and leucocyte differential were obtained using an Abbott Celldyn 3700 analyzer (Abbott, USA). NLR was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. MLR was calculated by dividing the absolute number of monocytes by the absolute number of lymphocytes. PLR was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes.

Study endpoint

The primary endpoint was long term all-cause mortality. Mortality was assessed using data from the Romanian Public Healthcare Insurance System, accessed in August 2024.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 23 (IBM Corp. in Armonk, NY, USA) and Epi InfoTM 7.2.5.0 2007 (CDC, Atlanta, GA, USA).

Numerical variables were stated as mean ± standard deviation if they had Gaussian distribution, or as median [interquartile range], otherwise. Categorial variables were stated as absolute numbers and percentages representing the frequency of the variable among the total number of patients.

For the inclusion of NT-proBNP in the multivariable analysis, we applied the log base 10 transformation to the original values of the biomarker.

In order to define the cut-off levels for the hematological ratios we used the lower limit of the highest tertile. Elevated values were considered those included in the third tertile of each ratio. Therefore, continuous variables were converted into dichotomous ones and included in the multivariable analysis for prediction of the primary endpoint.

For the assessment of association with the primary endpoint of continuous or dichotomous variables we used ROC analysis, and Yates' corrected chi-square test, respectively. After the initial analysis of association with the outcome, the parameters that were associated with all-cause mortality were included in the multivariable regression model to determine the independent predictors of all-cause mortality.

Survival analysis included multiple steps of multivariable regression. The first step included the parameters

correlated with the endpoint in the univariable analysis, to determine the independent predictors and the baseline predictive model for the endpoint. The independent predictors were then included, in a stepwise approach, in the multivariable analysis together with the hematological ratios, to determine their independent predictive value, as well as their additional value to the predictive model. The last step of the multivariable analysis included the baseline model and the hematological ratios that exhibited independent predictive value in the previous steps. Chi square analysis was used to determine the additional predictive value of each hematological ratio supplementary to the baseline model. A *p* value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Our cohort included 238 INOCA patients, of which 62.3% were female. The mean age of the cohort was 64.1 ± 9.5 years. Of all participants, 40.3% had acute coronary syndromes. The most prevalent cardiovascular risk factors were arterial hypertension (85.3%) and dyslipidemia (76.9%) (Table 1).

Heart failure was diagnosed in half of the patients, as well as chronic kidney disease (CKD). Close to 80% of participants were under therapy with statins, betablockers and ACEI/ARB, as opposed to nitrate and calcium channel blocker treatment that was prescribed to only one fifth of the cohort. Two thirds of patients were receiving either single or double antiplatelet therapy (Table 1).

Univariable and multivariable analysis of risk factors for all-cause mortality

A total of 35 patients (14.3%) reached the primary endpoint of all-cause mortality during the mean follow-up period of 5.8 ± 1.1 years.

Age, diabetes mellitus, atrial fibrillation (AF), heart failure (HF), and severe valvular disease were associated with an increased risk of all-cause mortality. Single antiplatelet therapy (SAPT) and betablocker therapy were associated with a lower risk of long-term all-cause mortality (Table 2).

Among laboratory parameters, higher NT-proBNP levels and the upper tertile of NLR and MLR were associated with all-cause mortality, whereas the highest tertile of PLR was not (Table 2).

In the multivariable analysis of the factors previously identified to increase the risk of all-cause mortality, age and heart failure were independent predictors of the outcome (Table 3).

Prognostic role of the hematological parameters in the multivariable predictive model

We derived the baseline predictive model for all-cause long-term mortality including age and heart failure. In a stepwise approach we then included the 3rd tertile of NLR, MLR and PLR in the multivariable survival analysis. NLR and MLR had independent and additive predictive value in this analysis and in the final mortality prediction model. The predictive power of the model increased progressively with the addition of NLR, MLR, and both parameters, respectively (Table 4).

Table 1. Cohort baseline characteristics (n=238)

	General characteristics
Age (years)	64.04 ± 9.50
Female patients (n, %)	148 (62.18%)
	Primary endpoint
All-cause mortality (n, %)	35 (14.31%)
Follow-up (years)	5.77 ± 1.14
	Cardiovascular risk factors
Arterial hypertension (n, %)	203 (85.29%)
Dyslipidemia (n, %)	183 (76.89%)
Diabetes mellitus (n, %)	72 (30.25%)
Active smoking (n, %)	27 (11.34%)
	Coronary syndrome on admission
ACS (n, %)	96 (40.34%)
CCS (n, %)	127 (53.36%)
PST (n, %)	87 (36.55%)
	Comorbidities
PAD (n, %)	15 (6.3%)
HF (n, %)	133 (55.88%)
AF (n, %)	55 (23.21%)
CKD (n, %)	115 (48.32%)
SVD (n, %)	16 (6.72%)
	Biological profile
NT-proBNP* (pg/mL)	1402.65 ± 566.79
HbA1C (%)	6.81 ± 1.43
Total cholesterol (mg/dL)	168.55 ± 49.16
LDL cholesterol (mg/dL)	91.43 ± 44.25
eGFR (mL/min/1.73m^2)	86.97 ± 19.65
NLR	2.35 [1.79–3.39]
3rd tertile NLR cut-off value	>2.99
MLR	0.28 [0.24–0.39]
3rd tertile MLR cut-off value	>0.36
PLR	125.84 [99.0 –165.74]
3rd tertile PLR cut-off value	>149.31
	Pharmacotherapy
SAPT (n, %)	141 (59.24%)
DAPT (n, %)	19 (7.98%)
Statins (n, %)	217 (91.18%)
Betablockers (n, %)	184 (77.31%)
ND-CCB (n, %)	40 (16.81%)
ACEI/ ARB (n, %)	192 (80.67%)
Nitrates (n, %)	48 (20.17%)

Abbreviations: ACEI/ARB- angiotensin converting enzyme inhibitors/aldosterone receptor blockers, ACS - acute coronary syndrome, AF- atrial fibrillation, CCS- chronic coronary syndrome, CKD- chronic kidney disease, D/SAPT- dual/ single antiplatelet therapy, eGFR- estimated glomerular filtration rate, HbA1c- glycated hemoglobin, HF- heart failure, MLR- monocyte-to-lymphocyte ratio, ND-CCB- non-dihydropyridine calcium channel blockers NLR- neutrophil-to-lymphocyte ratio, PAD- peripheral artery disease, PLR- platelet-to-lymphocyte ratio, PST- positive stress test, SVD- severe valve disease. *Measured in 173 patients.

Table 2. Univariable analysis of all-cause mortality predictors (n=238)

	General characteristics	*p* value
Age	1.10 (1.06 – 1.17)	<0.001
Female	0.68 (0.33 – 1.41)	0.29
CV risk factors		
AHT	1.99 (0.58 – 6.91)	0.27
Dyslipidemia	1.02 (0.43 – 2.39)	0.96
DM	2.54 (1.22 – 5.28)	0.01
Active smoking	1.37 (0.48 – 3.89)	0.55
CS on admission		
ACS	1.13 (0.55 – 2.33)	0.74
CCS	0.53 (0.26 – 1.10)	0.09
Comorbidities		
PAD	2.52 (0.68 – 7.52)	0.19
HF	3.73 (1.56 – 8.94)	0.003
AF	3.52 (1.66 – 7.46)	0.001
CKD	2.17 (0.84 – 5.57)	0.11
SVD	3.99 (1.35 – 11.82)	0.01
Biological profile		
Log_{10}NT-proBNP*	3.28 (1.68 – 6.40)	<0.001
3rd tertile NLR	4.33 (2.04 – 9.18)	<0.001
3rd tertile MLR	4.34 (2.05 – 9.19)	<0.001
3rd tertile PLR	1.42 (0.68 – 2.96)	0.36
HbA1C	0.92 (0.59 – 1.42)	0.70
Total cholesterol	0.99 (0.99 – 1.01)	0.77
LDL-cholesterol	1.01 (0.99 – 1.02)	0.78
eGFR	0.98 (0.97 – 1.01)	0.06
Pharmacotherapy		
SAPT	0.35 (0.17 – 0.73)	0.005
DAPT	0.66 (0.15 – 3.01)	0.59
Statins	0.71 (0.22 – 2.24)	0.56
Betablockers	0.37 (0.17 – 0.78)	0.01
ND-CCB	1.29 (0.52 – 3.19)	0.59
ACEI/ ARB	0.95 (0.39 – 2.34)	0.91
Nitrates	0.47 (0.16 – 1.39)	0.17

Results are expressed as odds ratios (OR) with 95% confidence interval. Abbreviations: ACEI/ARB- angiotensin converting enzyme inhibitors/aldosterone receptor blockers, ACS- acute coronary syndrome, AF- atrial fibrillation, AHT- arterial hypertension, CCS- chronic coronary syndrome, CKD- chronic kidney disease, CS- coronary syndrome, CV- cardiovascular, DAPT-dual antiplatelet therapy, DM- diabetes mellitus, eGFR-estimated glomerular filtration rate, HbA1c- glycated hemoglobin, HF- heart failure, LDL-low density lipoprotein, MLR- monocyte-to-lymphocyte ratio, ND-CCB- non-dihydropyridine calcium channel blockers, NLR- neutrophil-to-lymphocyte ratio, PAD- peripheral artery disease, PLR- platelet-to-lymphocyte ratio, SAPT- single antiplatelet therapy, SVD- severe valve disease. *Measured in 173 patients.

Table 3. Multivariable analysis of all-cause mortality predictors (n=238)

	HR (95% CI)	*p* value
Age	1.09 (1.04–1.15)	<0.001
HF	3.31 (1.29–8.51)	0.01
AF	2.21 (0.94–5.22)	0.07
SVD	2.94 (0.84–10.29)	0.09
DM	1.84 (0.81–4.14)	0.14

Abbreviations: AF- atrial fibrillation, CI-confidence interval, DM- diabetes mellitus, HF- heart failure, HR-hazard ratio, SVD- severe valve disease.

DISCUSSION

Our research evaluated the predictive role of three hematological ratios derived from the complete blood count, namely NLR, MLR and PLR for all-cause long-term mortality of patients with INOCA. Our key findings showed that 1) NLR and MLR, but not PLR, were independently associated with all-cause long-term mortality; 2) Adding NLR >2.99 and MLR >0.36 to age and heart failure diagnosis significantly improved the prediction model for the primary outcome.

To the extent of available data, this is one of the earliest studies to evaluate and compare NLR, MLR and PLR in their association to all-cause mortality in INOCA patients monitored after a mean follow-up period of 5.8 ± 1.1 years. The three hematological ratios were all previously studied concomitantly for the short and long-term prognosis of heart failure [18–21], acute coronary syndromes [22,23], and ST-segment elevation myocardial infarction [24]. In these settings they were associated with higher in-hospital as well as long-term all-cause death in heart failure [18–21], rehospitalization for acute decompensated heart failure, cardiac and all-cause mortality in ACS [23], and with higher thrombotic burden as well as increased risk of major cardiovascular events and all-cause mortality in patients with STEMI [24]. Moreover, in a recent systematic review, a bidirectional relationship between NLR and cardiovascular events was proven [25]. Patients with ACS, MI or stroke had higher values of the biomarker compared to the general population, and concomitantly, patients with increased NLR values had an increased risk of developing coronary artery disease, ACS, stroke or composite cardiovascular events, with a pooled OR ranging from 1.62 to 3.86 [25].

NLR and MLR in INOCA patients

Inflammation plays a pivotal role in the intricate pathophysiology of INOCA, alongside traditional cardiovascular risk factors as well as sympathetic dysfunction and hormonal dysregulation, with important clinical as well as prognostic implications [26]. Patients with microvascular angina have higher NLR, PLR, C-reactive protein, TNF-α and IL-6 levels [27]. Moreover, in women with INOCA, inflammatory markers were associated with the risk of heart failure hospitalizations and all-cause mortality [28]. Similar hematological ratios linked to systemic inflammation, respectively white blood cell count to mean platelet volume ratio and neutrophil-to-platelet ratio were also correlated with increased risk of major adverse cardiovascular outcomes including cardiovascular death, heart failure, nonfatal myocardial infarction, angina rehospitalization or stroke in a cohort of 274 MINOCA patients [29].

Table 4. Multivariable predictive model with hematological parameters (n=238)

	HR (95% CI)	*p* value	*p* value (added step)	Chi square	*p* value for Chi square
Baseline model				33.00	<0.001
Age	1.12 (1.06–1.18)	<0.001			
HF	3.78 (1.52–9.42)	0.004			
Baseline model + NLR				46.44	<0.001
Age	1.11 (1.05–1.17)	<0.001			
HF	4.83 (1.83–12.75)	0.001			
3rd tertile NLR	4.58 (1.99–10.55)	<0.001	<0.001		
Baseline model + MLR				47.18	<0.001
Age	1.12 (1.06–1.178)	<0.001			
HF	4.79 (1.80–12.76)	0.002			
3rd tertile MLR	4.74 (2.05–10.94)	<0.001	<0.001		
Baseline model + PLR				35.41	<0.001
Age	1.12 (1.06–1.18)	<0.001			
Hf	4.39 (1.70–11.34)	0.002			
3rd tertile PLR	1.94 (0.84–4.48)	0.11	0.12		
Baseline model + NLR + MLR				51.08	<0.001
Age	1.11 (1.05–1.17)	<0.001			
HF	5.27 (1.93–14.36)	0.001			
3rd tertile NLR	2.65 (1.01–7.00)	0.049	<0.001		
3rd tertile MLR	2.89 (1.10–7.66)	0.032	0.031		

Abbreviations: CI- confidence interval, HF- heart failure, HR- hazard ratio, MLR- monocyte-to-lymphocyte ratio, NLR- neutrophil-to-lymphocyte ratio, PLR- platelet-to-lymphocyte ratio.

NLR, as an indirect inflammatory marker, was among the first hematological indices to be evaluated in relation to coronary artery disease severity and prognosis. Across the spectrum of CAD ranging from atherosclerosis to chronic and acute coronary syndromes, NLR was associated with disease extension and survival [30]. In both CCS and ACS higher NLR values were correlated with a worse prognosis and in ACS patients elevated NLR levels were also associated with larger infarct size and myocardial remodeling leading to heart failure [30]. Recent data confirmed the prognostic role of NLR in patients with MINOCA. Gürdal et al. found NLR to be higher in patients with MINOCA compared to controls with normal coronary angiograms, and to be correlated with long-term mortality in these patients [31]. Similar to these findings, NLR was also a predictor of all-cause long-term mortality in our cohort of patients with both INOCA and MINOCA, as proven by the multivariable regression.

A recent meta-analysis concluded that both NLR and PLR are increased in patients with coronary syndrome X compared to healthy controls, reflecting the involvement of systemic inflammation [27], however the association with outcomes varies between the two biomarkers. In a sample of 72 MINOCA patients and 248 controls without coronary artery disease, Gürdal et al. also found only NLR to be correlated with survival outcomes, as opposed to PLR which was not associated with the end point [31].

MLR was associated with plaque vulnerability in patients with stable angina [32] and with major cardiovascular outcomes in patients with both acute as well as chronic coronary syndromes [33], however we found no previous data regarding its prognostic role in INOCA. In this study MLR had independent predictive value for all-cause mortality in patients with chronic or acute INOCA.

NLR and MLR cut-off values

The rising interest in the association of NLR and MLR with morbi-mortality in different patient populations was also reflected in the concern to define the normal values of these ratios. While no definitive cut-offs were established, observations about their variability in the general population were documented.

NLR values >2.26 defined the upper tertile of the biomarker, which was used as a cut-off for the survival analysis in a retrospective study of the NHANES population. Patients with NLR >2.26 had an increased rate of cardiovascular events and all-cause mortality [34]. In the same NHANES cohort higher MLR was also associated with all-cause and cardiovascular mortality [35]. The cut-off used was MLR >0.30, representing the lower limit of the third tertile in this sample of the general US population [35].

In a large prospective study including a sample of the US general population, mean ± standard deviation NLR for increasing quartiles ranged from 1.20 ± 0.20 (lower quartile) to 1.80 ± 0.10 (second quartile) to 2.30 ± 0.20 (third quartile) to 3.70 ± 1.40 (highest quartile) [36]. In the same study increasing NLR quartiles were associated with higher risk of overall mortality, as well as mortality due to heart disease, pulmonary pathology, kidney disease or malignancy, strengthening the hypothesis that inflammation and dysregulated immune pathways may play a major role in these associations [36]. The Rotter-

dam Study reported similar correlations of increasing NLR values with all-cause, cardiovascular as well as non-cardiovascular mortality in the general population, with the cut-off value NLR >2.41 for the highest quintile [37].

Cut-off values for NLR ranging from 1.80 to 2.60 were associated with coronary artery disease, from 2.18 to 5.70 with acute coronary syndromes and from 1.20 to 3.67 with composite outcomes in a recent meta-analysis [25]. Regarding the correlation of NLR with mortality of patients with acute coronary syndromes, another systematic review reported mean ± standard deviation NLR values ranging from 3.88 ± 0.58 to 13.78 ± 5.91 as predictors for the survival outcome [38]. Moreover, NLR levels were dependent on the underlying pathology, increasing with the severity and acute nature of the condition [38]. Patients without ischemic heart disease (IHD) had lower NLR compared to those with stable angina, while those with chronic coronary syndromes had lower values compared to acute coronary syndromes [38]. Therefore, in the context of ischemic coronary disorders, different cut-offs for NLR and, by extrapolation, for MLR, should be characterized for different clinical settings. Among the varied spectrum of IHD, we might argue the intermediate placing of INOCA that accounts for the NLR and MLR cut-offs correlated with increased mortality found in our study, above those found in the general population and in stable coronary disease, and below those found in patients with myocardial infarction.

Clinical utility of NLR and MLR

NLR and MLR reflect both the low-level chronic inflammation involved in the development and progression of INOCA [7,8], as well as the cardiovascular risk factor burden of these patients [25]. Their role in identifying patients at higher risk of long-term mortality may facilitate implementation of closer follow-up, more aggressive prevention strategies and improved risk factor correction.

A complex clinical syndrome and a significant health concern, INOCA is associated with an increased risk of major cardiovascular adverse events. Optimized risk stratification strategies still represent an unmet need for these patients [26]. In this setting, our study strengthens the utility of auxiliary inflammatory biomarkers such as NLR and MLR.

Limitations

We acknowledge several limitations to our research. While the retrospective design may limit the number of parameters included in the analysis, it allowed the long-term follow-up of survival, which was our primary endpoint. Data was collected from a single center; however, we argue that patient diversity was insured by the high addressability from multiple surrounding medical units in the region towards the university hospital.

CONCLUSIONS

In patients with acute or chronic INOCA, NLR and MLR were independently correlated with all-cause mortality. The most accurate mortality prediction model included NLR >2.99, MLR >0.36, age, and the diagnosis of heart failure.

ABBREVIATIONS

ACEI/ARB - angiotensin-converting enzyme inhibitors/ aldosterone receptor blockers

AF- atrial fibrillation

ACS- acute coronary syndrome

AISI- a surrogate index of systemic inflammation

CKD- chronic kidney disease

DAPT- dual antiplatelet therapy

eGFR- estimated glomerular filtration rate

ESC- European Society of Cardiology

HbA1c- glycated hemoglobin

HF- heart failure

ICA- invasive coronary angiography

IHD- ischemic heart disease

IL-6- interleukin 6

INOCA- ischemia with non-obstructive coronary arteries

LHR- lymphocyte-to-HDL cholesterol ratio

LDL- low-density lipoprotein

MACE- major adverse cardiovascular events

MHR- monocyte-to-HDL cholesterol ratio

MINOCA - myocardial infarction with non-obstructive coronary arteries

MLR- monocyte-to-lymphocyte ratio

NHR- neutrophil-to-HDL cholesterol ratio

NLR- neutrophil-to-lymphocyte ratio

PAD- peripheral artery disease

PHR- platelet-to-HDL cholesterol ratio

PLR- platelet-to-lymphocyte ratio

SAPT- single antiplatelet therapy

SII- systemic immune inflammation index

SIRI- systemic inflammation response index

TNF-α- tumor necrosis factor alpha

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AUTHORS' CONTRIBUTION

DEM: conceptualization, methodology, data curation, writing draft, review and preparation, project administration.

CD: conceptualization, methodology, formal analysis, data curation, writing draft, review and preparation.

CAB: conceptualization, methodology, writing review and preparation.

GAD: conceptualization, methodology, writing review and preparation, project administration.

CONFLICT OF INTEREST

None to declare.

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