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EVALUATION OF MARKERS OF CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH STEMI, NSTEMI, AND NONOBSTRUCTIVE CHRONIC CORONARY DISEASE, AND OF MORTALITY PREDICTORS

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CONCEPTUAL FRAMEWORK OF THE RESEARCH

Relevance of the topic. Acute myocardial infarction with ST-segment elevation (STEMI) or without ST-segment elevation (NSTEMI), both forms of acute coronary syndrome (ACS), is associated with high mortality and contributes to mortality among patients with ischemic heart disease and cardiovascular disease in general. Although several cross-sectional and prospective studies indicate that 12-month mortality among patients with STEMI and NSTEMI has decreased by 36–55% over recent decades, predicting outcomes and optimizing individualized post-infarction treatment remain challenges [1, 2]. Studies evaluating predictors of mortality risk in STEMI and NSTEMI have yielded inconsistent results [3, 4]; consequently, there is still no universally accepted prediction algorithm. The pathophysiological mechanisms explaining the similar mortality of STEMI and NSTEMI patients have not been fully elucidated, even though these biological patterns of myocardial infarction differ in ischemic preconditioning and considerably in the extent of necrosis. Clarifying this issue would advance pathophysiological concepts and help develop an algorithm to guide individualized post-infarction pharmacotherapy. In this context, the role of myocardial reperfusion injury deserves attention: according to pathophysiological evidence from basic studies, it contributes to expansion of the necrotic area following restoration of coronary blood flow. In the concept proposed by Gerd Heusch, this injury is related to ischemic preconditioning [5, 6]. Few clinical studies have investigated this relationship in patients with STEMI and NSTEMI during reperfusion following angioplasty, when its effects peak after 24 hours.

In addition to factors influencing mortality risk in STEMI and NSTEMI (such as age, sex, arterial hypertension, diabetes mellitus, myocardial hypertrophy and fibrosis) and the effects of myocardial reperfusion, coronary microvascular dysfunction (CMD) is an important mechanism. It is reported in up to 70% of patients, with approximately equal proportions of preprocedural cases (before revascularization) and postprocedural cases (triggered by microthromboembolism as a consequence of angioplasty). The diffuse myocardial ischemia, particularly in the subendocardial region, that persists after revascularization impairs myocardial energy and functional status and adversely affects post-infarction outcomes, including the risks of major adverse cardiovascular events (MACE) and death [7–9].

CMD is also an important pathogenetic mechanism underlying anginal episodes and myocardial ischemia in patients without obstruction (less than 50%) of the major epicardial arteries, described as angina with nonobstructive coronary arteries (ANOCA) and ischemia with nonobstructive coronary arteries (INOCA) in nonobstructive chronic coronary disease (noCCD). Moreover, CMD is reported in up to 70% of patients with noCCD, as in STEMI and NSTEMI. This underpins the growing interest in CMD as a diagnostic, prognostic and therapeutic target in ischemic myocardial disorders. The 2024 European guidelines for the management of chronic coronary syndromes specifically address CMD in relation to these targets, discussing its pathophysiological endotypes and highlighting the importance of individualized therapy [10]. CMD cannot be diagnosed by conventional coronary angiography alone and requires noninvasive or invasive functional investigations, which may be complex and expensive, including magnetic resonance imaging, positron emission tomography, and testing with acetylcholine, VIP and adenosine. Given the similar prevalence of CMD in STEMI, NSTEMI and noCCD, its pathophysiological basis can reasonably be assumed to share common features. Identifying them could support a useful diagnostic and predictive algorithm based on a multimarker strategy, an important approach to improving medical assessment. In a large meta-analysis by X. Zhang et al. (2023), encompassing studies that evaluated 216 machine-learning models for predicting mortality in ACS based on clinical, functional and metabolic indicators (e.g., blood glucose and creatinine), the authors drew two conclusions: (1) biomarkers may improve long-term mortality prediction, and (2) they may support identification of therapeutic targets [11]. A multimarker panel used in STEMI, NSTEMI and noCCD to identify mortality predictors and markers potentially informative of CMD should include key markers reflecting underlying pathogenetic mechanisms, such as inflammation, endothelial and hemostatic dysfunction, NETosis, oxidative stress, cellular injury,

neuroendocrine activation and cardiovascular remodeling. Our experience with the multimarker strategy and review of the literature demonstrate the importance of established markers and the potential of new markers for meaningful assessment of cardiovascular diseases [12]. These emerging markers include heart-type fatty acid-binding protein (H-FABP), neopterin, neprilysin, endocan and syndecans, the von Willebrand factor/ADAMTS13 ratio, platelet microvesicles and zonulin. Particular emphasis should be placed on markers of NETosis (neutrophil elastase, MMP-8 and myeloperoxidase), two indicators of neuroendocrine activity (the Ang 1–7/Ang II ratio and agonistic autoantibodies against endothelin-1 ETA receptors expressed on vascular smooth muscle cells and cardiomyocytes), and atherogenicity markers (paraoxonase-1, oxidized HDL and angiopoietin-2). Recent studies have identified agonistic autoantibodies against ET-1 and Ang II receptors (ETA and AT1, respectively) in patients with various cardiovascular conditions accompanied by altered immune status (e.g., rheumatoid arthritis, lupus and allergies). Their serum levels correlate with the severity of disturbed circulatory homeostasis.

On this basis, the following research aim was formulated:

To assess a multimarker panel in patients with STEMI, NSTEMI and nonobstructive chronic coronary disease in order to identify markers with high predictive value for 12-month mortality, evaluate the severity of myocardial reperfusion injury, and identify markers potentially useful in the diagnosis of coronary microvascular dysfunction.

Study objectives:

1. To determine the 12-month mortality rate among patients with STEMI and NSTEMI.
2. To assess admission multimarker panel characteristics in STEMI patients who survived and those who died within 12 months.
3. To assess admission multimarker panel characteristics in NSTEMI patients who survived and those who died within 12 months.
4. To identify admission biomarkers predictive of 12-month mortality in STEMI and NSTEMI by calculating odds ratios and the area under the receiver operating characteristic curve (AUC).
5. To compare myocardial reperfusion injury in deceased and surviving patients with STEMI and NSTEMI by evaluating changes in biomarker levels at 24 hours in the context of the fundamental Heusch concept.
6. To compare multimarker panel characteristics in surviving and deceased STEMI and NSTEMI patients seven days after angioplasty, a period characterized pathophysiologically by declining inflammation and the onset of post-infarction myocardial remodeling.
7. To assess admission multimarker panel changes in patients with noCCD and identify the most pronounced increases and decreases relative to controls, which may suggest CMD from a pathophysiological perspective.
8. To develop algorithms for predicting 12-month mortality in STEMI and NSTEMI and coronary microvascular dysfunction in noCCD, with the aim of optimizing individualized treatment.

Research hypotheses:

- Application of the multimarker panel, considered an important component of the noninvasive assessment of CMD [13, 14], will identify CMD-associated markers and their underlying pathophysiological mechanisms, particularly when instrumental diagnostic options in noCCD are limited.
- A comprehensive multimarker panel encompassing the principal pathogenetic mechanisms of unfavorable post-infarction progression will enable identification of mortality predictors in STEMI and NSTEMI.

Overview of the research methodology and justification of the selected methods.

The methodological approach is based on meta-analyses and prospective studies highlighting the importance of identifying CMD in ACS and especially noCCD, in which CMD is an important pathogenetic mechanism underlying clinical progression. The multimarker panel is relevant for several reasons:

Greater accessibility compared with invasive or noninvasive instrumental investigations.
Capacity to identify the responsible pathophysiological mechanisms and events.
The possibility of using identified predictors to substantiate therapeutic targets and optimize individualized treatment.

Moreover, predicting 12-month mortality risk after revascularization in patients with STEMI and NSTEMI using markers identified through the multimarker panel extends the utility of this approach to prognostic assessment and the development of therapeutic strategies in the post-infarction period. Statistical methods for evaluating the predictive value of the markers, including ROC curve analysis and odds-ratio calculation, allow their performance to be assessed.

Scientific novelty and originality of the research

Application of a panel comprising 44 established and new markers to identify mortality predictors in patients with STEMI and NSTEMI.

For the first time in the Republic of Moldova, the pathophysiological significance of emerging markers—agonistic autoantibodies against ET-1 ETA receptors, the Ang 1–7/Ang II ratio, neprilysin, endocan and platelet vesicles—was evaluated in relation to the course of STEMI, NSTEMI and CMD. The proatherogenic status of patients with STEMI, NSTEMI and noCCD was assessed by combining paraoxonase-1, oxidized HDL and angiopoietin-2 measurements. A precise method was developed to determine circulating oxidized HDL levels, reflecting impaired HDL capacity for removing cholesterol from foam cells within the neointima. Agonistic autoantibodies against ET-1 ETA receptors were identified in deceased STEMI and NSTEMI patients. New evidence was obtained on the role of IL-1β and soluble IL-6 receptors (sIL-6R) in the inflammatory response and mortality prediction in STEMI and NSTEMI. Myocardial tolerance to ischemia–reperfusion in survivors and nonsurvivors with STEMI and NSTEMI was evaluated in the context of the Heusch concept, which links the severity of ischemia with myocardial tolerance to reperfusion as established in basic research. An algorithm for predicting CMD in noCCD patients was developed.

Major problem addressed in the field

Application of the multimarker panel identified markers with potential diagnostic value for CMD in noCCD and markers with high predictive power for the risk of death within 12 months of revascularization in STEMI and NSTEMI patients. This enables identification of key pathophysiological determinants and optimization of individualized treatment.

Theoretical significance of the findings

Analysis of changes in circulating markers of major pathogenetic mechanisms of disturbed circulatory homeostasis yielded novel evidence for the roles of inflammation, endothelial dysfunction and NETosis in post-infarction progression and mortality risk. The contribution of primary hemostatic disturbances to CMD was identified, together with increased von Willebrand factor/ADAMTS13 ratios and circulating platelet microparticles. The pathophysiological concept of neuroendocrine activation in STEMI and NSTEMI was extended by documenting a reduced Ang 1–7/Ang II ratio and increased neprilysin levels correlated with the decline in Ang 1–7, confirming the endopeptidase's capacity to degrade this heptapeptide. A plausible mechanism linking impaired immune status with mortality risk was demonstrated through the presence of agonistic autoantibodies against ET-1 ETA receptors. A novel mechanism of atherogenicity and its impact in STEMI and NSTEMI was highlighted: elevated oxidized HDL and angiopoietin-2 combined with reduced paraoxonase-1. Dysbiosis was also implicated in STEMI and NSTEMI progression, with lipopolysaccharides and zonulin as associated markers.

The findings in STEMI and NSTEMI patients undergoing angioplasty are consistent with the Heusch concept linking ischemic preconditioning to the severity of myocardial injury during reperfusion, primarily indicated by relative increases in the cellular injury markers H-FABP and ischemia-modified albumin. A plausible role for GDF-15 in predicting CMD in noCCD was confirmed. Significantly elevated angiopoietin-2 in noCCD, viewed as a marker of coronary arteriolar stiffness and impaired endothelium-dependent and endothelium-independent reactivity,

could increase coronary microvascular resistance, a key measurement in the instrumental diagnosis of CMD, and thus serve as a diagnostic marker.

Practical value of the findings

● A five-marker panel was proposed for predicting 12-month mortality after angioplasty in patients with STEMI and NSTEMI, based on ROC AUC values (IL-1β, soluble IL-6 receptors, endocan, NT-proBNP and MMP). Targeted pharmacological attenuation of the underlying pathogenetic mechanisms (inflammation, endothelial dysfunction and hemostatic dysfunction) may support investigation of individualized treatment options, such as monoclonal antibodies, gliflozins, GLP-1 receptor agonists and cilostazol.

● H-FABP was identified as a relevant marker of myocardial reperfusion injury in the context of the Heusch concept, along with a possible contribution of NETosis. Pharmacological inhibition of this process (e.g., colchicine during the acute infarction phase) could be investigated as an approach to limiting myocardial necrosis and mortality risk in STEMI and NSTEMI.

● A panel was proposed to investigate CMD in noCCD. Its markers may also help characterize pathophysiological endotypes and evaluate individualized treatment: IL-1β, soluble IL-6 receptors and angiopoietin-2 as markers of inflammation, endothelial dysfunction and stiffness; MMP and the von Willebrand factor/ADAMTS13 ratio as markers of impaired primary hemostasis; and GDF-15 as an integrated marker of inflammation, oxidative stress, endothelial dysfunction and coronary remodeling.

Dissemination and approval of scientific results: The scientific results obtained during the research were presented and discussed at several international specialist forums: the 61st National Congress of Cardiology, 21–24 September 2022, Sinaia, Romania, where the presented work received Second Prize; the European Society of Cardiology Congress, 25–28 August 2023, Amsterdam, Netherlands; the European Society of Cardiology Congress, 30 August–2 September 2024, London, United Kingdom; the 63rd National Congress of Cardiology, 18–21 September 2024, Sinaia, Romania; the European Society of Cardiology Congress jointly organized with the World Congress of Cardiology, 29 August–1 September 2025, Madrid, Spain; the 64th National Congress of Cardiology, 17–20 September 2025, Sinaia, Romania, where the presented work received Second Prize; the European Society of Cardiology Congress, 28–31 August 2026, Munich, Germany; and the 65th National Congress of Cardiology, 16–19 September 2026, Sinaia, Romania, where the scientific contribution was recognized with a diploma.

The research findings were also presented at international invention exhibitions: the 49th International Exhibition of Inventions of Geneva, 17–21 April 2024, Geneva, Switzerland, with the invention "The circulating endothelial progenitor cells – a predictor of coronary microcirculation disorder and major adverse cardiovascular events (MACE) in patients with acute myocardial infarction without ST segment elevation"; and the 50th International Exhibition of Inventions of Geneva, 9–13 April 2025, Geneva, Switzerland, with the invention "Circulating SR-Co-ATPase: an indicator of myocardial reperfusion injury and mortality risk after coronary angioplasty," which was awarded a gold medal.

Participation in prestigious international scientific events and the distinctions received at cardiology congresses and international invention exhibitions confirm the recognition and scientific relevance of the findings, as well as their potential application in medical practice.

Implementation of scientific results: The findings are being applied and used in subsequent research at the Institute of Cardiology and Novamed Multidisciplinary Hospital. They are also incorporated into teaching materials used in education and professional training at Nicolae Testemițanu State University of Medicine and Pharmacy.

Keywords: STEMI, NSTEMI, nonobstructive chronic coronary disease, multimarker panel, mortality prediction algorithm, diagnostic markers of coronary microvascular dysfunction.

Thesis-related publications: The research findings were reported in 48 scientific works, including one single-author monograph; two articles in scientific journals indexed in the international Web of Science and Scopus databases; 27 articles in journals included in the National Register of Specialist Journals, of which one was in a category B+ journal and 26 in category B journals; 16

abstracts and scientific papers published in supplements to the European Heart Journal and Romanian Journal of Cardiology in connection with national and international scientific congresses and conferences; and two inventions presented at the International Exhibitions of Inventions in Geneva (2024 and 2025), one of which received a gold medal in 2025.

1. PATHOPHYSIOLOGICAL CONSIDERATIONS REGARDING THE PREDICTION OF STEMI, NSTEMI, NONOBSTRUCTIVE CHRONIC CORONARY DISEASE, AND CORONARY MICROVASCULAR DYSFUNCTION

Post-infarction outcomes—particularly the long-term risk of MACE and mortality after revascularization in STEMI and NSTEMI—conceptually depend on several determinants: (1) the quality of myocardial remodeling preceding angioplasty; (2) the extent of ischemic myocardial necrosis and necrosis caused by the reperfusion syndrome; (3) the recovery of endothelial function, hemostasis, neuroendocrine activity and NETosis during resolution of the acute infarction phase, associated with the expression of anti-inflammatory M2 macrophages; and (4) coronary microvascular dysfunction (CMD). Preprocedural myocardial remodeling in STEMI and NSTEMI is closely linked to the infarct-related artery (left anterior descending, right coronary or circumflex artery), the severity of inflammation, endothelial and hemostatic dysfunction, oxidative stress and the neuroendocrine response [5, 9, 10]. These pathophysiological factors can be identified using specific circulating markers measured at admission.

Myocardial reperfusion injury, investigated in experimental studies, is associated with the calcium and oxygen paradoxes. However, interventions targeting these mechanisms do not sufficiently reduce reperfusion injury, a finding also attributed to NETosis, whose specific markers include neutrophil elastase, myeloperoxidase and MMP-8 [4, 5, 9]. In clinical settings, the severity of reperfusion injury in STEMI and NSTEMI can be estimated from the increase in markers of irreversible cardiomyocyte injury, together with NETosis markers, 24 hours after angioplasty compared with admission. One emerging cardiomyocyte injury marker is heart-type fatty acid-binding protein (H-FABP), considered more sensitive and specific than troponins. The acute course of myocardial infarction includes several decisive time points following revascularization: (1) 0–24 hours, corresponding to maximal neutrophil infiltration of the necrotic myocardium and initiation of NETosis; (2) 24–72 hours, characterized by proinflammatory M1 macrophage expression, producing a maximal inflammatory response after three days; and (3) 5–7 days, a period of maximal anti-inflammatory M2 macrophage expression, reflected by increased IL-14, IL-10 and growth factors (e.g., FGF-21 and TGF-1β). The day-seven biomarker profile may indicate the risk of pathological myocardial remodeling by the end of the subsequent period (5–6 months after angioplasty), characterized by an increase of more than 20% in left ventricular end-diastolic pressure and volume. CMD, observed in both ACS and noCCD, is associated with reduced coronary flow reserve (less than 2) and an increased microvascular resistance index (greater than 25) in arterioles measuring 100–500 μm. Several pathophysiological patterns or endotypes can be distinguished: coronary microspasm due to impaired endothelium-dependent and endothelium-independent responses to vasoactive factors (e.g., acetylcholine, adenosine, Ang II and ET-1); coronary arteriolar remodeling manifested by vessel-wall thickening on a background of endothelial dysfunction triggered and sustained by inflammation and oxidative stress; and a thrombotic state manifested by microthrombi resulting from embolization of thrombotic material from the atherosclerotic plaque after angioplasty and disturbances of primary hemostasis [15–17]. The key diagnostic parameters of CMD—coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR)—are accurately measured by invasive and/or noninvasive instrumental tests, which may be complex and costly.

In this context, the multimarker panel may be investigated as a complementary tool for CMD assessment because it permits (1) repeated measurements, (2) identification of pathogenetic mechanisms, and (3) potential development of diagnostic and predictive algorithms and improvement of cardiovascular risk scores.

2. MATERIALS AND METHODS

In accordance with the study objectives, the research comprised a retrospective clinical study, an analytical observational cohort study, and a basic research study. The retrospective component involved analysis of a 67-marker panel measured in STEMI and NSTEMI patients in two prospective projects conducted from 2016 to 2024 at the Institute of Cardiology. Of the 67 markers, 44 were selected based on their association with the principal pathogenetic mechanisms:

- Inflammation (IL-1β, IL-6, soluble IL-6 receptor, TNF-α, hsCRP, IL-10, neopterin and E-selectin).
- Endothelial dysfunction (endocan, endothelial microparticles, nitric oxide, angiopoietin-2 and endothelial progenitor cells).
- Hemostasis (fibrin monomers, platelet microparticles and von Willebrand factor/ADAMTS13).
- NETosis (neutrophil elastase, myeloperoxidase and MMP-8).
- Cellular injury (H-FABP and ischemia-modified albumin).
- Neuroendocrine activity (copeptin, adrenomedullin, catestatin, NT-proBNP, Ang 1–7/Ang II, neprilysin and agonistic anti-ETA autoantibodies).
- Oxidative stress and dysbiosis (NOX2, malondialdehyde, PPOA; zonulin and LPS).
- Cardiovascular remodeling (galectin-3, MMP-2, MMP-9, FGF-21, FGF-23, GDF-15, TGF-1β and syndecan-1).
- Atherogenicity (Lp(a), oxidized HDL and paraoxonase-1).

The retrospective study involved several stages:

1. Development of a questionnaire containing more than 150 items to extract detailed clinical and paraclinical information from archived records of 558 STEMI patients and 614 NSTEMI patients during hospitalization, including risk factors and comorbidities.
2. Identification of all cardiovascular deaths in both the STEMI and NSTEMI cohorts during the 12 months following primary myocardial revascularization.
3. Selection of 44 markers from the available panel of 66 markers measured at different stages of STEMI and NSTEMI progression (admission and 24 or 72 hours, 7 days, and 1, 3, 6 and 12 months after revascularization).

The 12-month mortality rate was 16.3% in STEMI (91 of 558 patients) and 15.5% in NSTEMI (95 of 614 patients). To identify markers predictive of death in STEMI and NSTEMI, two equal groups of nonsurvivors were assembled based on two main criteria: cardiac death and availability of marker measurements at three assessment points (admission, 24 hours and day seven after angioplasty). These comprised 80 of the 91 deceased STEMI patients and 80 of the 95 deceased NSTEMI patients. The survivor (reference) groups were likewise equal and selected from the total of 986 patients who survived 12 months: 80 of the 467 STEMI survivors and 80 of the 519 NSTEMI survivors. Selection criteria aimed to achieve the greatest possible homogeneity between the four groups, assessed using the chi-square test for:

- age, sex and family history;
- prevalence of risk factors;
- prevalence of comorbidities;
- clinical manifestations;
- number of treated culprit coronary arteries;
- stent type;
- functional class of heart failure;
- periprocedural therapy. Exclusion criteria for the survivor and nonsurvivor groups were:
- absence of marker data at one or more of the three assessment points (admission, 24 hours and day seven);
- uncertain cause of death;

acute or chronic infections potentially affecting the validity of biomarker results. The control group comprised 60 apparently healthy individuals in whom the same 44 markers were measured.

Thus, the retrospective study comprised two groups of deceased patients with STEMI and NSTEMI, two groups of survivors with STEMI and NSTEMI, and a control group (Table 1).

Table 1. Retrospective study groups used to assess the multimarker panel

Group	STEMI	NSTEMI
Total	558	614
Deaths at 12 months	91 (16,3%)	95 (15,5%)
Nonsurvivors included in the study	80	80
Survivors at 12 months	467	519
Survivors included in the study	80	80

Markers were assessed at 24 hours by calculating their relative increase compared with admission levels to evaluate the effects of reperfusion on the myocardium (the Heusch phenomenon). For this purpose, markers were selected that, according to the pathophysiological concept of the reperfusion paradox and its contribution to postischemic myocardial injury, could help evaluate the Heusch concept:

- Markers of myocardial ischemia and injury (H-FABP, ischemia-modified albumin).
- Markers of endothelial injury and activation of primary hemostasis (endothelial microparticles, endocan and platelet microparticles).
- Markers of inflammation and NETosis (IL-1β, MMP-8, neutrophil elastase and myeloperoxidase).
- Marker of coronary microvascular dysfunction (GDF-15).

Analysis of the multimarker panel seven days after angioplasty, at the end of the acute infarction phase and the beginning of extracellular matrix remodeling, included changes in the 44 markers measured at admission. At this stage of post-infarction progression, the markers were also investigated as plausible predictors of CMD, given that the ischemia–reperfusion effects associated with an exaggerated inflammatory response and oxidative stress decline seven days after myocardial revascularization. The analytical observational cohort study involved application of the same multimarker panel to 80 noCCD patients selected from more than 160 patients diagnosed in accordance with European guideline criteria for nonobstructive chronic coronary disease: (i) clinical presentation, (ii) ECG and (iii) coronary angiography. Panel analysis aimed to identify markers with diagnostic value for CMD. Exclusion criteria were:

- MINOCA.
- Uncertain diagnosis.
- Previous myocardial infarction.
- Acute or chronic infections potentially affecting the validity of biomarker measurements.

The clinical study design is shown in Figure 1.

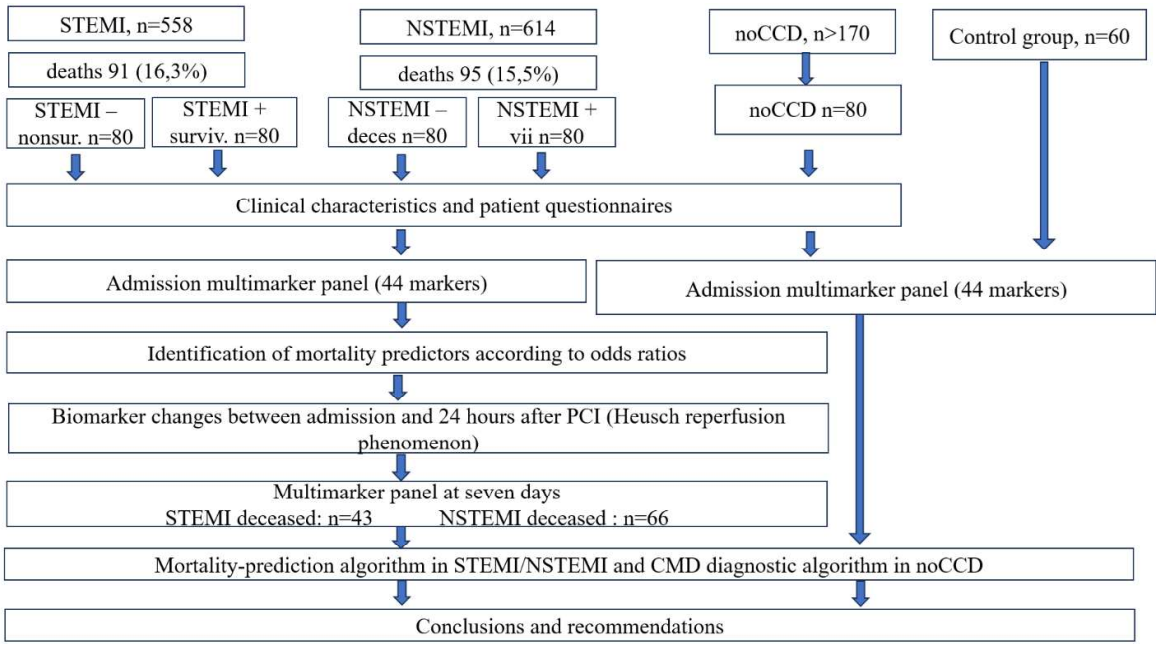


Figure 1. Clinical study design

Statistical processing of the data. Serum levels of all markers were entered in Excel to calculate:

- Mean (M)
- Standard deviation (SD)
- Median (Me)
- Maximum and minimum values
- 25th and 75th percentiles
- Student's t statistic
- p value ($p < 0.05$ indicating statistical significance).

The association between biomarker levels and patient death within 12 months after angioplasty was assessed by calculating the odds ratio (OR) and analyzing the area under the receiver operating characteristic curve (AUC). Odds ratios, 95% confidence intervals (CIs) and p values were calculated using OpenEpicom.com and its "Two-by-Two Table" feature for medical studies. The median of the overall sample (nonsurvivors plus survivors) was used as the cutoff. The ROC curve was constructed from sensitivity (the true-positive rate) and specificity (the true-negative rate). The x-axis represents the false-positive rate (1 − specificity) and the y-axis represents sensitivity. The area under the ROC curve (AUC), ranging from 0 to 1 or 0% to 100%, indicates the marker's discriminative capacity. An AUC of 90–100% denotes excellent predictive power; 80–89% indicates good or high predictive power. Below 60% (0.6), predictive performance for mortality is poor, while an AUC of 50% indicates no discrimination.

3. CLINICAL COURSE AND HOMOGENEITY OF THE STUDY GROUPS OF PATIENTS WITH STEMI AND NSTEMI

The prevalence of the main cardiovascular risk factors in the study groups is presented in Table 2.

Table 2. Prevalence of cardiovascular risk factors in the study groups

Risk factor	Survivors STEMI, n=80	Nonsurvivors STEMI, n=80	Survivors STEMI, n=80	Nonsurvivors STEMI, n=80
Arterial hypertension	94%	92,6%	94,7%	96,8%
Hypercholesterolemia	67.5%	56,8%	75,8%	78,9%
Diabetes mellitus	26%	36%	28,2%	34,9%
Previous myocardial infarction	15,4%	30%	51,1%	49,5%
Stroke	3,6%	11,7%	15,8%	23,4%
Killip 4	1%	27,4% p<0,05	7,4%	15,6%
Two culprit coronary arteries	13,6%	17,6%	0%	6,9% p<0,05

Deceased STEMI patients had a significantly higher frequency of Killip class 4; differences were also noted in the presence of two affected coronary arteries.

4. MULTIMARKER PANEL ASSESSMENT IN PATIENTS WITH STEMI AND NSTEMI: SURVIVORS VERSUS NONSURVIVORS

4.1. Multimarker panel assessment at admission in STEMI patients

Analysis of inflammatory markers revealed significant differences between nonsurvivors and survivors for three markers: IL-1β, soluble IL-6 receptor and E-selectin (Table 3). All markers in the study groups differed significantly from those in the control group.

Table 3. Circulating inflammatory marker levels at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
IL-1β, pg/ml	5,13±0,68	7,17±0,69 p<0,001 vs control	8,99±1,16 p<0,001 vs control	<0,05
IL-6, pg/ml	4,36±0,64	7,34±0,79 p<0,001 vs control	7,67±0,97 p<0,001 vs control	>0,05
Soluble IL-6 receptor, pg/ml	1,24±0,35	2,62±0,60 p<0,001 vs control	3,96±1,87 p<0,001 vs control	<0,05
IL-10, pg/ml	7,77±0,98	3,71±0,74 p<0,001 vs control	3,81±0,74 p<0,001 vs control	>0,05
TNF-alpha, pg/ml	5,85±0,92	9,50±0,76 p<0,001 vs control	9,62±1,23 p<0,001 vs control	>0,05
hgCRP, mg/L	1,45±0,41	7,90±0,74 p<0,001 vs control	8,29±0,94 p<0,001 vs control	>0,05
E-selectin, ng/ml	64,36±7,93	95,07±4,71 p<0,001 vs control	103,22±15,17 p<0,001 vs control	<0,05
Neopterin, nM/L	3,48±0,72	4,89±0,86 p<0,001 vs control	4,89±0,85 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Regarding endothelial dysfunction, significant differences between nonsurvivors and survivors were observed for endothelial microparticles, nitric oxide and angiopoietin-2 (Table 4).

As with inflammatory markers, all the markers investigated differed significantly from control levels.

Table 4. Circulating markers of endothelial dysfunction at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
MPE (CD144+), count/mL	148,58±10,46	328,09±37,58 p<0,001 vs control	349,60±63,39 p<0,001 vs control	=0,0049
Endocan, ng/ml	1,27±0,41	3,58±0,61 p<0,001 vs control	3,78±0,95 p<0,001 vs control	=0,053
NO, μM/L	74,21±8,47	50,65±7,77 p<0,001 vs control	47,63±8,81 p<0,001 vs control	=0,011
Angiopoietin-2, pg/ml	2146,07±122,94	3289,65±350,29 p<0,001 vs control	3576,06±463,89 p<0,001 vs control	=0,039
Endothelial progenitor cells, count/μL	499,15±63,40	327,47±12,69 p<0,001 vs control	314,57±30,86 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

All three specific NETosis markers were significantly higher than in controls, but no statistically significant differences were identified between study groups (Table 5).

Table 5. Circulating NETosis marker levels at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
MMP-8, ng/ml	28,81±6,45	53,62±6,53 p<0,001 vs control	54,21±6,65 p<0,001 vs control	>0,05
EN, ng/ml	16,16±4,14	31,56±4,71 p<0,001 vs control	32,62±4,62 p<0,001 vs control	>0,05
MPO, U/ml	29,25±5,87	74,84±11,61 p<0,001 vs control	75,16±11,03 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Hemostasis was impaired in both groups according to the markers examined; however, levels were significantly higher in nonsurvivors than in survivors (Table 6).

Table 6. Circulating hemostasis marker levels at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
MPP, CD62P, 1/μL	161,37±16,85	319,08±84,19 p<0,001 vs control	429,05±149,21 p<0,001 vs control	<0,001
von Willebrand factor/ AMDATS13, arbitrary units	1,26±0,38	2,78±1,46 p<0,001 vs control	3,68±2,16 p<0,001 vs control	<0,001
Fibrin monomers, mg/ml	4,54±0,63	8,41±1,03 p<0,001 vs control	9,21±0,99 p<0,001 vs control	<0,01

Legend: p_1 – significance compared with STEMI survivors

In nonsurvivors, however, markers of cellular injury and myocardial ischemia did not differ from the corresponding markers in survivors (Table 7).

Table 7. Circulating markers of myocardial ischemia and injury at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
IMA, mkg/dl	1,81±0,55	5,96±1,90 p<0,001 vs control	6,08±1,91 p<0,001 vs control	>0,05
H-FABP, ng/ml	1,73±0.69	8,21±2,24 p<0,001 vs control	8,97±2,67 p<0,001 vs control	>0,05
Adrenomedullin, pg/ml	12,82±2,99	32,11±5.92 p<0,001 vs control	34,43±6,57 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Neuroendocrine activity was characterized by a significant 20.9% reduction in the Ang 1–7/Ang II ratio in nonsurvivors versus survivors and a 44.9% increase in NT-proBNP (Table 8). In addition, agonistic anti-ETA receptor autoantibodies were detected in 20 patients but were absent from group 1.

Table 8. Circulating markers of neuroendocrine activity at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
Neprilysin, ng/ml	0,49±0,38	1,99±0,82 p<0,001 vs control	1,95±1,63 p<0,001 vs control	>0,05
Ang 1-7/Ang II, arbitrary units	0,88±0,14	0,62±0,25 p<0,001 vs control	0,49±0,28 p<0,001 vs control	<0,001
AAET-AR, ng/dL	0	0	3,64±3,24 p<0,001 vs control (positive in 20 patients)	—
NT-Pro-BNP, pg/ml	142,44±17,25	402,74±182,80	583,44±127,75 p<0,001 vs control	<0,001
Copeptin, pmol/L	18,16±2,42	31,27±5,16	36,17±9,17 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Myocardial remodeling was present in both groups, with all seven principal markers differing significantly from control values. Moreover, GDF-15 and FGF-21 were significantly higher in nonsurvivors than in survivors from group 1 (Table 9).

Table 9. Circulating cardiovascular remodeling marker levels at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
GDF-15, ng/ml	1,29±0,44	2,86±0,82 p<0,001 vs control	3,71±1,74 p<0,001 vs control	<0,001
FGF-21, pg/ml	64,29±5,76	92,21±9,94 p<0,001 vs control	98,94±10,41 p<0,001 vs control	<0,05
TGF-β, ng/ml	4,85±0,87	8,15±1,13 p<0,001 vs control	8,21±1,38 p<0,001 vs control	>0,05
Syndecan-1, ng/ml	125,86±7,39	261,50±36,17 p<0,001 vs control	264,47±40,21 p<0,001 vs control	>0,05
Galectin-3, ng/ml	3,52±0,78	7,66±1,78 p<0,001 vs control	7,78±1,79 p<0,001 vs control	>0,05
MMP-2, ng/ml	2,95±0,77	4,92±1,30 p<0,001 vs control	5,12±0,79 p<0,001 vs control	>0,05
MMP-9 ng/ml	14,71±2,64	21,73±3,79 p<0,001 vs control	22,89±3,67 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

A major feature in STEMI, among both nonsurvivors and survivors, was activation of oxidative stress and dysbiosis together with increased atherogenicity. These markers differed significantly from controls but not between patient groups (Table 10). Of particular note, oxidized HDL increased 2.89-fold in survivors and 2.94-fold in nonsurvivors, associated with a 41–42% decrease in paraoxonase-1.

Table 10. Markers of dysbiosis, oxidative stress and atherogenicity at admission

Marker	Control (n=60), M±SD	STEMI survivors (n=80), M±SD	STEMI deaths (n=80), M±SD	p_1
LpS, pg/ml	12,46±2,71	21,14±5,53 p<0,001 vs control	22,18±5,54 p<0,001 vs control	>0,05
Zonulin, ng/ml	1,76±0,57	3,61±1,04 p<0,001 vs control	3,85±1,09 p<0,001 vs control	>0,05
NOX-2, pg/ml	21,64±4,54	37,35±5,48 p<0,001 vs control	39,28±6,13 p<0,001 vs control	>0,05
MDA, µmol/L	4,42±0,64	7,32±1,14 p<0,001 vs control	7,62±0,83 p<0,001 vs control	>0,05
AOPP, µmol/L	41,83±4,53	71,91±14,26 p<0,001 vs control	73,92±10,26 p<0,001 vs control	>0,05
Paraoxonase-1, nM/mL	421,55±25,14	241,37±40,74 p<0,001 vs control	246,97±41,58 p<0,001 vs control	>0,05
Oxidized HDL, arbitrary units	1,0±0,15	2,89±0,85 p<0,001 vs control	2,94±0,88 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

4.2. Multimarker panel assessment at admission in NSTEMI patients

Assessment of the admission multimarker panel in survivors and nonsurvivors with NSTEMI revealed changes also observed in STEMI. Inflammatory marker levels differed significantly from controls, while circulating IL-1β and soluble IL-6 receptor levels were significantly higher in nonsurvivors (Table 11).

Table 11. Circulating inflammatory marker levels at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
IL-1β, pg/ml	5,13±0,68	7,12±0,66 p<0,001 vs control	8,91±1,81 p<0,001 vs control	<0,05
IL-6, pg/ml	4,36±0,64	7,15±1,55 p<0,001 vs control	7,44±1,58 p<0,001 vs control	>0,05
Soluble IL-6 receptor, pg/ml	1,24±0,35	2,66±0,78 p<0,001 vs control	3,84±0,55 p<0,001 vs control	<0,01
IL-10, pg/ml	7,77±0,98	3,98±1,72 p<0,001 vs control	3,97±0,59 p<0,001 vs control	>0,05
TNF-alpha, pg/ml	5,85±0,92	9,24±1,17 p<0,001 vs control	9,45±0,97 p<0,001 vs control	>0,05
hsCRP, mg/L	1,45±0,41	7,85±0,87 p<0,001 vs control	8,11±0,68 p<0,001 vs control	>0,05
E-selectin, ng/ml	64,36±7,93	101,31±14,95 p<0,001 vs control	106,32±21,72 p<0,001 vs control	>0,05
Neopterin, nM/L	3,48±0,72	4,59±0,86 p<0,001 vs control	4,69±1,09 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Notably, the serum level of the principal inflammatory marker, hsCRP, did not differ significantly between groups, as in STEMI. Endothelial dysfunction was similarly associated with significantly altered NO and angiopoietin-2 levels in nonsurvivors. In contrast to STEMI, however, endocan was significantly higher in nonsurvivors than in survivors, whereas endothelial microparticle levels were similar (Table 12).

Table 12. Circulating markers of endothelial dysfunction at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
MPE (CD144+), count/mL	148,58±10,46	282,97±59,86 p<0,001 vs control	286,84±52,61 p<0,001 vs control	>0,05
Endocan, ng/ml	1,27±0,41	3,55±0,70 p<0,001 vs control	3,95±1,07 p<0,001 vs control	=0,0284
NO, μM/L	74,21±8,47	51,49±11,27 p<0,001 vs control	48,53±10,85 p<0,001 vs control	=0,0462
Angiopoietin-2, pg/ml	2146,07±122,94	3367,95±153,19 p<0,001 vs control	3483,36±457,36 p<0,001 vs control	=0,0174
Endothelial progenitor cells, count/μL	499,15±63,40	333,61±63,34 p<0,001 vs control	321,59±55,96 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

As in STEMI, NETosis markers were similar between NSTEMI groups and significantly higher than in controls (Table 13).

Table 13. Circulating NETosis marker levels at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
MMP-8, ng/ml	28,81±6,45	52,57±6,53 p<0,001 vs control	53,88±8,11 p<0,001 vs control	>0,05
EN, ng/ml	16,16±4,14	32,82±9,21 p<0,001 vs control	33,77±6,94 p<0,001 vs control	>0,05
MPO, U/ml	29,25±5,87	62,83±13,94 p<0,001 vs control	64,77±13,11 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Hemostasis was clearly impaired in NSTEMI as well. Unlike STEMI, however, fibrin monomers, which were nearly twice as high as in controls, did not differ between groups (Table 14). From a pathophysiological perspective, the 2.73-fold and 2.78-fold increases in the von Willebrand factor/ADAMTS13 ratio among survivors and nonsurvivors, respectively, are important; this is an emerging marker of primary hemostasis.

Table 14. Circulating hemostasis marker levels at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
MPP, CD62P, 1/μL	161,37±16,85	304,94±92,03 p<0,001 vs control	428,29±165,47 p<0,001 vs control	<0,001
von Willebrand factor/ AMDATS13, arbitrary units	1,26±0,38	2,34±0,92 p<0,001 vs control	3,18±1,19 p<0,001 vs control	<0,001
Fibrin monomers, mg/ml	4,54±0,63	8,42±2,07 p<0,001 vs control	8,69±1,13 p<0,001 vs control	=0,1558

Legend: p_1 – significance compared with STEMI survivors

As in STEMI, cellular injury markers did not differ significantly between the NSTEMI groups (Table 15).

Table 15. Markers of myocardial ischemia and injury

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
IMA, mkg/dl	1,81±0,55	5,38±1,65 p<0,001 vs control	5,36±1,36 p<0,001 vs control	>0,05
H-FABP, ng/ml	1,73±0.69	7,19±2,24 p<0,001 vs control	7,42±2,67 p<0,001 vs control	=0,2174
Adrenomedullin, pg/ml	12,82±2,99	30,78±5.53 p<0,001 vs control	32,33±6,11 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Adrenomedullin, assessed as a marker of ischemia and endothelial cell activity, was more than 2.5 times higher than in controls. Notably, NT-proBNP, a marker of heart failure, was similar between NSTEMI groups (Table 16), whereas in STEMI it was significantly elevated in

nonsurvivors. Agonistic anti-ETA receptor autoantibodies were detected in 16 deceased NSTEMI patients. The Ang 1–7/Ang II ratio was also 20.9% lower in nonsurvivors than in survivors.

Table 16. Circulating neuroendocrine activity marker levels at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
Neprilysin, ng/ml	0,49±0,38	2,07±0,67 p<0,001 vs control	1,98±0,81 p<0,001 vs control	>0,05
Ang 1-7/Ang II, arbitrary units	0,88±0,14	0,67±0,44 p<0,001 vs control	0,53±0,32 p<0,001 vs control	<0,01
AAET-AR, ng/dL	0	0	3,64±3,24 p<0,001 vs control (positive in 16 patients)	—
NT-Pro-BNP, pg/ml	142,44±17,25	514,12±99,01	513,39±119,06	>0,05
Copeptin, pmol/L	18,16±2,42	28,12±10,53	31,61±4,66	>0,05

Legend: p_1 – significance compared with STEMI survivors

At admission, the quantitative profile of cardiovascular remodeling markers in NSTEMI was similar to that in STEMI. Likewise, serum GDF-15 and FGF-21 were significantly elevated in nonsurvivors relative to controls (Table 17).

Table 17. Circulating cardiovascular remodeling marker levels at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
GDF-15, ng/ml	1,29±0,44	2,67±0,81 p<0,001 vs control	3,82±1,88 p<0,001 vs control	<0,001
FGF-21, pg/ml	64,29±5,76	91,66±11,54 p<0,001 vs control	96,63±14,94 p<0,001 vs control	=0,0102
TGF-β, ng/ml	4,85±0,87	7,31±1,12 p<0,001 vs control	7,67±1,18 p<0,001 vs control	>0,05
Syndecan-1, ng/ml	125,86±7,39	246,74±36,17 p<0,001 vs control	250,47±23,85 p<0,001 vs control	>0,05
Galectin-3, ng/ml	3,52±0,78	6,71±2,01 p<0,001 vs control	6,61±1,83 p<0,001 vs control	>0,05
MMP-2, ng/ml	2,95±0,77	4,61±1,42 p<0,001 vs control	4,85±1,11 p<0,001 vs control	>0,05
MMP-9, ng/ml	14,71±2,64	22,56±4,86 p<0,001 vs control	20,87±3,80 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

Oxidized HDL was increased 2.78-fold in survivors and 2.84-fold in nonsurvivors, accompanied by significantly reduced paraoxonase-1, particularly among nonsurvivors (a 48% reduction; Table 18). These changes in atherogenicity markers were associated with activation of oxidative stress, manifested by elevated malondialdehyde and advanced oxidation protein products. As in STEMI, dysbiosis was present in NSTEMI, reflected by significantly increased lipopolysaccharides and zonulin.

Table 18. Markers of dysbiosis, oxidative stress and atherogenicity at admission

Marker	Control (n=60), M±SD	NSTEMI survivors (n=80), M±SD	NSTEMI deaths (n=80), M±SD	p_1
LpS, pg/ml	12,46±2,71	21,84±3,45 p<0,001 vs control	23,36±9,22 p<0,001 vs control	>0,05
Zonulin, ng/ml	1,76±0,57	3,88±1,91 p<0,001 vs control	3,58±0,88 p<0,001 vs control	>0,05
NOX-2, pg/ml	21,64±4,54	36,87±8,74 p<0,001 vs control	38,16±5,23 p<0,001 vs control	>0,05
MDA, µmol/L	4,42±0,64	7,10±1,11 p<0,001 vs control	7,32±1,09 p<0,001 vs control	>0,05
AOPP, µmol/L	41,83±4,53	70,77±13,98 p<0,001 vs control	74,52±10,81 p<0,001 vs control	>0,05
Paraoxonase-1, nM/mL	421,55±25,14	237,30±40,56 p<0,001 vs control	219,20±42,60 p<0,001 vs control	=0,0033
Oxidized HDL, arbitrary units	1,0±0,15	2,78±0,93 p<0,001 vs control	2,84±0,89 p<0,001 vs control	>0,05

Legend: p_1 – significance compared with STEMI survivors

4.3. Multimarker panel assessment 24 hours after angioplasty (the reperfusion effect in the context of the Heusch concept) in STEMI and NSTEMI patients

According to the concept proposed by Gerd Heusch, reperfusion effects are closely but indirectly related to ischemic preconditioning, so more severe myocardial ischemia is associated with a less pronounced reperfusion effect. Therefore, analysis of biomarker changes from admission to 24 hours may reveal new pathophysiological aspects of reperfusion in STEMI and NSTEMI survivors and nonsurvivors and identify predictors of mortality risk. From the multimarker panel analyzed at admission, we selected markers conceptually most closely linked to the reperfusion effect:

Markers of myocardial ischemia and injury (H-FABP and ischemia-modified albumin).

Markers of endothelial injury and primary hemostasis activation (endothelial microparticles, endocan and platelet microparticles).

Markers of inflammation and NETosis (IL-1β, MMP-8, neutrophil elastase and myeloperoxidase).

Marker of coronary microvascular dysfunction (GDF-15). H-FABP, the principal marker of irreversible myocardial injury, increased after 24 hours in all study groups compared with admission (Table 19).

Table 19. Relative increases (%) in marker levels 24 hours after admission

Marker	STEMI survivors	STEMI nonsurvivors	NSTEMI survivors	NSTEMI nonsurvivors
H-FABP, ng/ml	42,03±6,81	85,14±10,10 p<0,01	48,83±14,93	104,3±23,75 p<0,01; p1<0,01
IMA, mkg/dl	39,65±6,25	65,55±10,16 p<0,01	40,18±14,93	88,49±15,85 p<0,01; p1<0,01

Legend: p – significance compared with survivors; p_1 – significance compared with STEMI nonsurvivors

Two important findings deserve emphasis:

1. Among nonsurvivors, the relative increase was significantly greater than among survivors.

2. In NSTEMI nonsurvivors, the increase in H-FABP was 25.5% greater than in STEMI nonsurvivors. This evidence of lower myocardial tolerance to reperfusion may help explain the similar mortality rates in NSTEMI and STEMI. Similarly to H-FABP, ischemia-modified albumin rose substantially more in nonsurvivors than survivors in both STEMI and NSTEMI.

Importantly, the increase in this marker was significantly greater in NSTEMI nonsurvivors than in STEMI nonsurvivors (88.49% versus 65.55%). Myocardial reperfusion injury is clearly manifested by worsening endothelial and hemostatic dysfunction. In our study, changes in endothelial microparticles, endocan and platelet microparticles at the peak reperfusion effect were consistent with the greater increase in H-FABP among NSTEMI nonsurvivors (Table 20).

Table 20. Relative increases (%) in marker levels 24 hours after admission

Marker	STEMI survivors	STEMI nonsurvivors	NSTEMI survivors	NSTEMI nonsurvivors
MPE, count/mL	34,33±8,89	51,22±6,04 p<0,01	48,21±9,88	63,23±9,78 p<0,01; p1<0,05
Endocan, ng/ml	38,76±4,30	52,81±7,66 p<0,01	37,08±8,86	75,64±8,67 p<0,01; p1<0,01
MPP, CD62P, 1/μL	31,14±6,85	54,25±9,14 p<0,01	32,87±7,18	72,73±9,46 p<0,01; p1<0,01

Legend: p – significance compared with survivors; p_1 – significance compared with STEMI nonsurvivors

Thus, in NSTEMI nonsurvivors, the increases in these markers were significantly greater than in STEMI nonsurvivors—by 23.4%, 43.2% and 34.1%, respectively. The more persistent endothelial dysfunction and primary hemostatic disturbances 24 hours after restoration of coronary blood flow in NSTEMI are compatible with the Heusch concept linking myocardial reperfusion tolerance to ischemic preconditioning. To evaluate the contribution of NETosis to myocardial reperfusion injury, we assessed changes in its specific markers (Table 21).

Table 21. Relative increases (%) in NETosis markers and IL-1β after 24 hours

Marker	STEMI survivors	STEMI nonsurvivors	NSTEMI survivors	NSTEMI nonsurvivors
MMP-8, ng/ml	46,08±10,66	68,99±13,79 p<0,01	46,96±6,61	79,78±7,31 p<0,01;p1<0,05
Neutrophil elastase, ng/ml	49,27±6,99	77,41±8,27 p<0,01	51,69±8,876	89,85±7,60 p<0,01; p1<0,05
MPO, U/ml	44,02±13,32	69,27±8,45 p<0,01	48,95±6,73	79,74±9,05 p<0,01; p1<0,05
IL-1β, pg/ml	30,13±4,92	52,36±7,88 p<0,01	31,65±6,76	53,06±7,86 p<0,01

Legend: p – significance compared with survivors; p_1 – significance compared with STEMI nonsurvivors

MMP-8, neutrophil elastase and myeloperoxidase all showed significantly greater increases 24 hours after revascularization in NSTEMI nonsurvivors than in STEMI nonsurvivors. NETosis activation was also observed among STEMI and NSTEMI survivors, but marker increases were smaller than among nonsurvivors. IL-1β increased similarly in survivors and nonsurvivors with STEMI and NSTEMI. Accordingly, reperfusion-triggered NETosis activation correlates with changes in H-FABP and may be regarded as a genuine mechanism of myocardial reperfusion injury, a predictor and a potential therapeutic target. The relative increase in circulating GDF-15 compared with admission was nearly identical in STEMI and NSTEMI nonsurvivors and

almost twice that seen in survivors. These observations therefore support the hypothesis that CMD contributes to post-infarction progression and mortality risk in STEMI and NSTEMI.

4.4. Multimarker panel assessment seven days after angioplasty in STEMI and NSTEMI patients

Evidence from several studies, including our research, indicates that inflammation (with expression of anti-inflammatory M2 macrophages) and oxidative stress decline seven days after revascularization for STEMI and NSTEMI. Post-infarction remodeling of the myocardium and extracellular matrix, together with the onset or exacerbation of CMD, therefore become key factors influencing the risk of MACE and especially death. Multimarker panel assessment in this setting may identify CMD predictors among patients who subsequently died during follow-up, since mechanical myocardial revascularization by angioplasty alleviates epicardial artery-related ischemia but does not eliminate the risk of microvascular ischemia. The principal inflammatory markers are shown in Table 22.

Table 22. Inflammatory markers in STEMI and NSTEMI patients seven days after angioplasty

Group	IL-1β	R-IL-6	IL-10	hsCRP	TNF-α
Control, n=60	5,13±0,68	1,24±0,35	7,77±0,98	1,45±0,41	5,85±0,92
STEMI survivors, n=80	6,77±0,79 p<0,05	1,73±0,71 p<0,05	6,57±0,91 p<0,05	4,31±0,76 p<0,001	6,71±0,78 p<0,05
STEMI deaths, n=43	8,15±0,88 p<0,01 p1<0,01	3,19±0,78 p<0,001 p1<0,01	4,44±0,63 p<0,001 p1<0,01	4,74±0,86 p<0,001	7,22±0,98 p<0,05
NSTEMI survivors, n=80	6,48±0,75 p<0,05	1,76±0,72 p<0,05	6,61±0,89 p<0,05	4,25±0,75 p<0,001	6,69±0,83 p<0,05
NSTEMI deaths, n=66	8,06±0,86 p<0,001 p1<0,01	3,24±0,93 p<0,01 p1<0,01	4,52±0,65 p<0,001 p1<0,01	4,92±0,87 p<0,001	7,19±0,92 p<0,05

Legend: p – significance compared with controls; p_1 – significance compared with survivors

Circulating IL-1β and soluble IL-6 receptor levels were nearly equal in STEMI and NSTEMI nonsurvivors and significantly higher than in survivors. Although IL-10 did not differ significantly between survivors and nonsurvivors at admission, a significant difference emerged by day seven, with an average 32.5% reduction among nonsurvivors. hsCRP was similar across all four groups, ranging from 4.31 to 4.92 mg/L. Endothelial dysfunction on day seven remained more pronounced in nonsurvivors than in survivors in both STEMI and NSTEMI (Table 23).

Table 23. Circulating endothelial dysfunction marker levels in STEMI and NSTEMI patients seven days after angioplasty

Group	MPE (CD144+)	Endocan	NO	Apo-2	CPE
Control, n=60	148,58±10,46	1,27±0,41	74,21±8,47	2146,07±122,94	499,15±63,40
STEMI survivors, n=80	157,22±21,24 p>0,05	1,91±0,63 p<0,05	67,93±8,29 p>0,05	2566,53±37,22 p<0,05	382,83±55,12 p<0,05
STEMI deaths, n=43	236,29±28,13 p<0,05 p1<0,05	2,88±0,85 p<0,05 p1<0,05	55,44±7,16 p<0,05 p1<0,05	2784,67±37,89 p<0,05	357,16±58,25 p<0,05
NSTEMI survivors, n=80	153,46±19,88 p>0,05	1,98±0,59 p<0,05	68,17±9,19 p>0,05	2496±36,45 p<0,05	391,34±49,62 p<0,05
NSTEMI deaths, n=66	241,15±27,61 p<0,05 p1<0,05	2,96±0,78 p<0,05 p1<0,05	58,84±8,43 p<0,05 p1<0,05	2885,12±36,35 p<0,05	357,16±58,25 p<0,05

Legend: p – significance compared with controls; p_1 – significance compared with survivors

A particularly important finding was the normalization of endothelial microparticle levels only in STEMI and NSTEMI survivors, although endocan remained significantly below control values. Endothelial progenitor cell levels also remained significantly reduced on day seven, without significant differences between survivors and nonsurvivors. Angiopoietin-2, a marker functionally linked to endothelial progenitor cells, likewise remained below control values without differing between groups. Given the role of NETosis in myocardial reperfusion injury, its specific marker levels on day seven are of interest, together with E-selectin, which reflects both inflammation and neutrophil infiltration (Table 24).

Table 24. Circulating NETosis markers and E-selectin in STEMI and NSTEMI patients on day seven

Group	MMP-8	Elastase	MPO	E-selectin
Control, n=60	28,81±6,45	16,16±4,14	29,25±5,87	64,36±7,93
STEMI survivors, n=80	37,14±4,16 p<0,05	18,83±3,66 p>0,05	38,72±6,77 p<0,05	70,72±9,36 p>0,05
STEMI deaths, n=43	43,78±5,83 p<0,01	27,44±5,42 p<0,01; p1<0,05	42,46±7,17 p<0,01	81,76±11,16 p<0,05; p1<0,05
NSTEMI survivors, n=80	38,85±4,27 p<0,05	19,47±3,83 p>0,05	39,17±6,42 p<0,05	71,65±10,24 p>0,05
NSTEMI deaths, n=66	45,62±5,56 p<0,01	28,79±5,36 p<0,01; p1<0,05	41,89±7,18 p<0,01	82,15±10,23 p<0,05; p1<0,05

Legend: p – significance compared with controls; p_1 – significance compared with survivors

Analysis showed no significant survivor–nonsurvivor differences in MMP-8 or myeloperoxidase, whereas differences persisted for neutrophil elastase and E-selectin. Thus, nonsurvivors retained a more pronounced inflammatory background than survivors even at the end of the acute myocardial infarction phase. E-selectin suggests both a “stressed” endothelium and activation of transvascular migration of polymorphonuclear leukocytes, to the detriment of favorable post-infarction myocardial remodeling. Hemostasis also remained impaired on day seven after reperfusion (Table 25).

Table 25. Circulating hemostasis marker levels in STEMI and NSTEMI patients seven days after angioplasty

Group	Fibrin monomers	Platelet microparticles, CD62P	von Willebrand factor/ AMDATS13
Control, n=60	4,54±0,63	161,37±16,85	1,26±0,38
STEMI survivors, n=80	5,88±1,48 p<0,01	339,52±80,16 p<0,01	2,26±1,19 p<0,01
STEMI deaths, n=43	6,83±1,85 p<0,001 p1<0,05	367,72±78,83 p<0,01 p1>0,05	2,91±1,31 p<0,01 p1<0,05
NSTEMI survivors, n=80	5,92±1,89 p<0,01	326,41±79,64 p<0,01	2,47±1,16 p<0,01
NSTEMI deaths, n=66	6,87±1,52 p<0,001; p<0,05	394,55±82,19 p<0,01; p1>0,05	2,96±1,34 p<0,01

Legend: p – significance compared with controls; p_1 – significance compared with survivors

Three findings are particularly noteworthy:

1. Fibrin monomers remained above control levels in STEMI and NSTEMI, with a significantly greater increase in nonsurvivors than in survivors.
2. The von Willebrand factor/ADAMTS13 ratio remained 28.8% higher in STEMI nonsurvivors than in survivors.
3. Platelet microparticle levels did not differ significantly between nonsurvivors and survivors.

Regarding neuroendocrine activity, neprilysin and the Ang 1–7/Ang II ratio differed significantly from controls on day seven in every group, in opposite directions: neprilysin increased more than threefold, while the Ang 1–7/Ang II ratio declined by 29.6–42.1% (Table 26). One possible explanation is that neprilysin cleaves Ang 1–7 more actively than the octapeptide Ang II.

Table 26. Circulating neuroendocrine activity markers in STEMI and NSTEMI patients seven days after angioplasty

Group	Neprilysin	Ang 1-7/Ang II	AAET-AR
Control, n=60	0,49±0,38	0,88±0,14	0
STEMI survivors, n=80	1,39±1,26 p<0,001	0,62±0,87 p<0,05	0
STEMI deaths, n=43	1,72±1,88 p<0,001	0,54±0,43 p<0,05	3,52±3,56 (n=11) p<0,001
NSTEMI survivors, n=80	1,33±1,18 p<0,001	0,61±0,72 p<0,05	0
NSTEMI deaths, n=66	1,64±1,23 p<0,001	0,51±0,22 p<0,05	5,27±4,54 (n=8) p<0,001

Legend: p – significance compared with controls

Growth factors and metalloproteinases are major mediators of cardiovascular remodeling, while galectin-3 is an established marker supported by several studies. According to the literature, growth differentiation factor-15 (GDF-15) is considered not only a marker of extracellular matrix expansion but also a CMD marker in patients with STEMI.

The highest GDF-15 levels on day seven were found in STEMI nonsurvivors (3.76 ± 0.94 ng/mL) and NSTEMI nonsurvivors (3.72 ± 0.93 ng/mL), significantly exceeding those of survivors (Table 27).

Table 27. Circulating cardiovascular remodeling marker levels in STEMI and NSTEMI patients seven days after angioplasty

Marker	Control	STEMI survivors	STEMI deaths	NSTEMI survivors	NSTEMI deaths
GDF-15, ng/ml	1,29±0,44	2,29±0,73 p<0,05	3,76±0,94 p<0,01; p1<0,05 (+64.2%)	2,23±0,62 p<0,05	3,72±0,93 p<0,01; p1<0,05 (+66.8%)
TGF-1β, ng/ml	4,85±0,87	5,28±1,34 p>0,05	6,41±1,83 p<0,05; p1>0,05	5,16±1,42 p>0,05	6,38±1,89 p<0,05; p1>0,05
Syndecan-1, ng/ml	125,86±7,39	174,23±19,58 p<0,05	198,66±22,16 p<0,05; p1>0,05	170,43±20,63 p<0,05	192,19±23,78 p<0,05; p1>0,05
Galectin-3, ng/ml	3,52±0,78	5,88±1,59 p<0,05	6,24±1,67 p<0,05; p1>0,05	5,77±1,52 p<0,05	6,08±1,61 p<0,05; p1>0,05
MMP-2, ng/ml	2,95±0,77	3,89±1,12 p<0,05	4,44±1,24 p<0,01; p1>0,05	3,76±1,16 p<0,05	4,58±1,27 p<0,01; p1>0,05
MMP-9, ng/ml	14,71±2,64	18,36±4,18 p<0,05	21,56±4,33 p<0,01; p1<0,05	18,22±4,14 p<0,05	20,49±4,12 p<0,01; p1<0,05

Legend: p – significance compared with controls; p₁ – significance compared with survivors

The other markers showed no significant survivor–nonsurvivor differences on day seven, except MMP-9 among NSTEMI nonsurvivors. Oxidative stress markers had declined from admission levels but remained significantly higher than in controls, without a conclusive difference between nonsurvivors and survivors (Table 28). Paraoxonase-1 followed a similar course.

Table 28. Circulating oxidative stress and atherogenicity markers in STEMI and NSTEMI patients seven days after angioplasty

Marker	Control	STEMI survivors	STEMI deaths	NSTEMI survivors	NSTEMI deaths
NOX-2, pg/ml	21,64±4,54	33,49±6,12 p<0,01	38,52±6,77 p<0,01; p1>0,05	32,47±6,23 p<0,01	39,28±6,37 p<0,01; p1>0,05
MDA, μmol/L	4,42±0,64	5,81±1,26 p<0,05	6,89±1,37 p<0,01; p1>0,05	5,72±1,28 p<0,05	6,73±1,29 p<0,01; p1>0,05
AOPP, μmol/L	41,83±4,53	59,63±10,72 p<0,01	72,52±14,11 p<0,01; p1>0,05	57,38±10,31 p<0,01	69,16±14,67 p<0,01; p1>0,05
Paraoxonase-1 nM/mL	421,55±25,14	283,42±40,71 p<0,01	254,61±40,16 p<0,01; p1>0,05	289,32±39,96 p<0,01	267,23±40,73 p<0,01; p1>0,05

Legend: p – significance compared with controls; p₁ – significance compared with survivors

4.5. Prediction of mortality in STEMI and NSTEMI patients using ROC curve analysis

The ROC curve for admission IL-1β in STEMI and NSTEMI patients is shown in Figure 2.

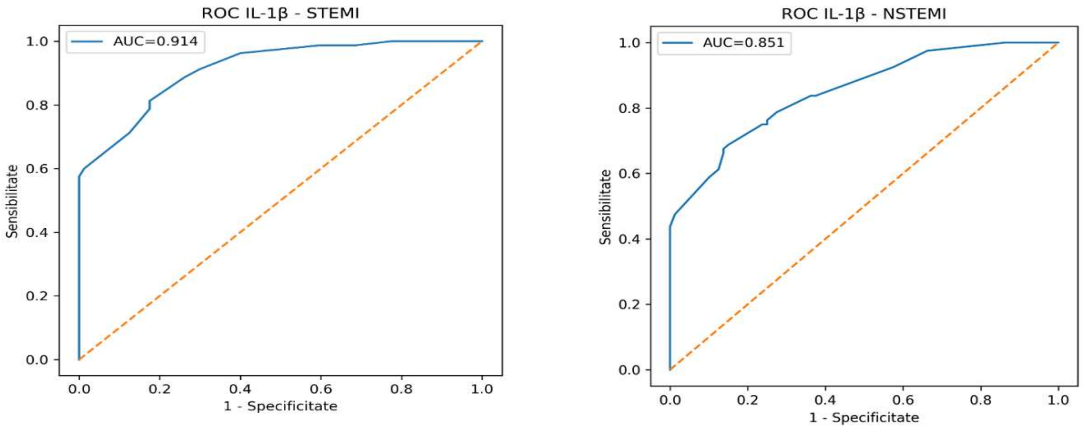


Figure 2. ROC curve for IL-1β in STEMI and NSTEMI patients

In STEMI, the AUC was 0.914, indicating excellent discrimination. Sensitivity and specificity ranged from 81.2% to 82.5% (Table 29). In NSTEMI, the AUC was 0.851, indicating high predictive power (within the 0.8–0.9 range). Sensitivity and specificity ranged from 67.5% to 86.2% (Table 29). The IL-1β cutoff for mortality prediction was ≥7.9 pg/mL in STEMI and ≥8.1 pg/mL in NSTEMI.

Table 29. ROC parameters for IL-1β in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity	Specificity	Accuracy
STEMI	0.914	≥ 7.90	81.2%	82.5%	81.9%
NSTEMI	0.851	≥ 8.10	67.5%	86.2%	76.9%

Another inflammatory marker, soluble IL-6 receptor, also predicted mortality risk. Its AUC was higher in NSTEMI (0.932), indicating excellent discrimination, than in STEMI (0.748), indicating moderate predictive power (Figure 3).

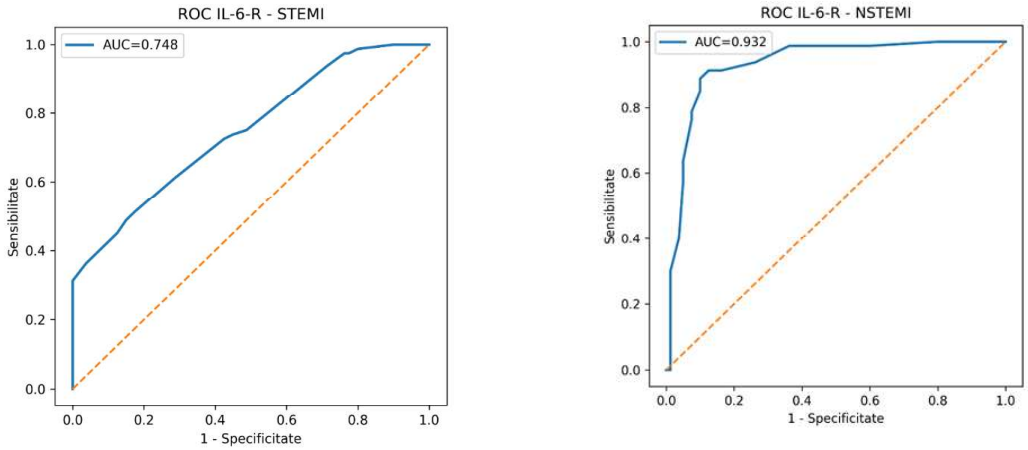


Figure 3. ROC curve for soluble IL-6 receptor in STEMI and NSTEMI patients

The corresponding sensitivity and specificity measures were also higher in NSTEMI (Table 30), ranging from 88.8% to 90%. Marker cutoffs were similar, at ≥3.3–3.4 pg/mL (Table 30).

Table 30. ROC parameters for soluble IL-6 receptor in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity	Specificity	Accuracy
STEMI	0.748	≥ 3.40	48.8%	85.0%	66.9%
NSTEMI	0.932	≥ 3.30	88.8%	90.0%	89.4%

The intensity of inflammation, both before and after its exacerbation by acute myocardial infarction, reflects the balance between pro- and anti-inflammatory markers, while hsCRP is an integrated indicator of the inflammatory response. In our study, hsCRP showed lower predictive power than IL-1β and soluble IL-6 receptor (Figure 4).

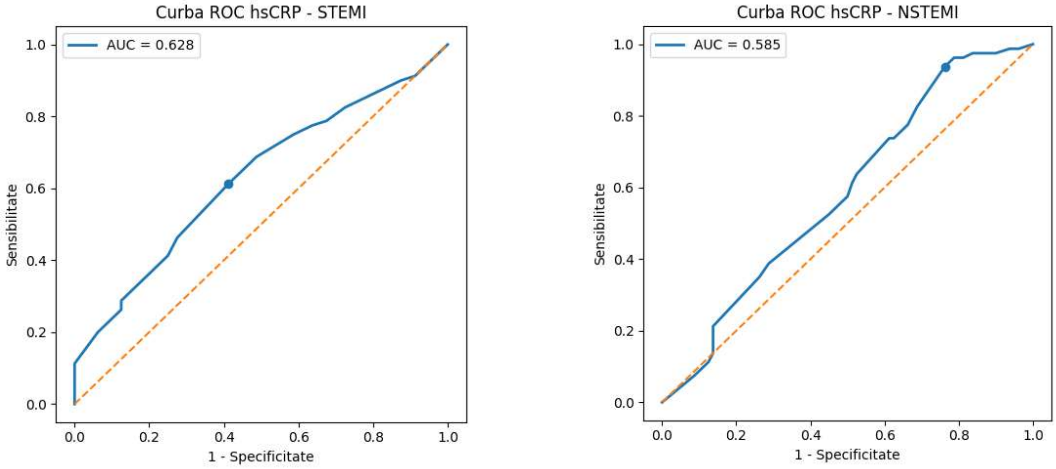


Figure 4. ROC curve for admission hsCRP in STEMI and NSTEMI patients

The AUC values indicate only modest discrimination by hsCRP between nonsurvivors and survivors, although performance was better in STEMI (0.628; poor to moderate) than NSTEMI (0.585; low). Notably, hsCRP sensitivity for predicting death in NSTEMI was high (93.8%; Table 31).

Table 31. ROC parameters for hsCRP in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity	Specificity
STEMI	0.628	≥ 8.3	61.3%	58.8%
NSTEMI	0.585	≥ 7.2	93.8%	23.8%

E-selectin plays an important role, mainly in neutrophil migration. Its predictive value for mortality was more evident in STEMI (Figure 5).

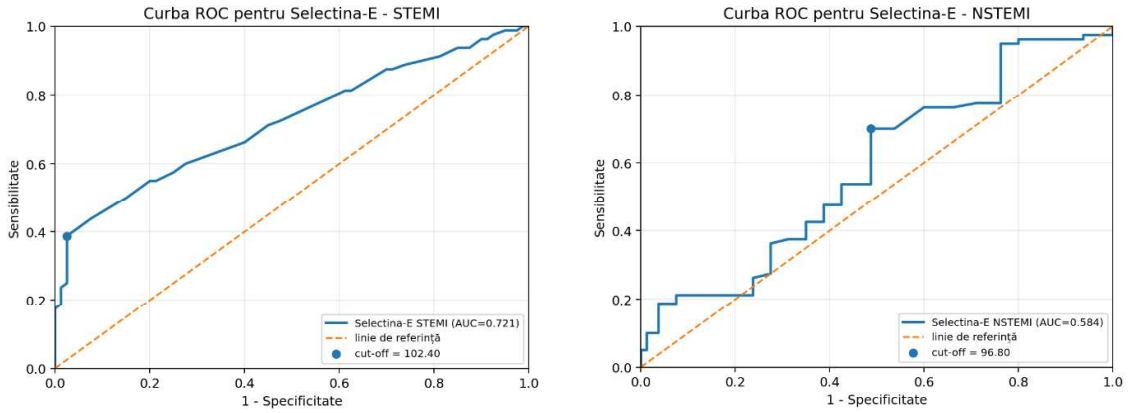


Figure 5. ROC curve for admission E-selectin in STEMI and NSTEMI patients

The AUC in STEMI was 0.721, indicating good to moderate discrimination for mortality prediction. The optimal Youden-index cutoff was E-selectin ≥102.40 ng/mL, with sensitivity of 38.75% and specificity of 97.50% (Table 32).

Table 32. ROC parameters for E-selectin in STEMI and NSTEMI patients

Group	AUC	AUC 95% CI	E-selectin cutoff	Sensitivity	Specificity	Youden J	p
STEMI	0.721	0.642–0.797	≥ 102.40	38.75%	97.50%	0.362	<0.001
NSTEMI	0.584	0.497–0.671	≥ 96.80	70.00%	51.25%	0.212	0.065

In NSTEMI, the AUC was 0.584 (95% CI 0.497–0.671), suggesting modest discrimination. The optimal threshold was E-selectin ≥96.80 ng/mL, with 70% sensitivity and 51.25% specificity. This finding was indicative only and did not reach statistical significance (p = 0.065). Nitric oxide had no demonstrable predictive value for mortality in either STEMI or NSTEMI (Figure 6).

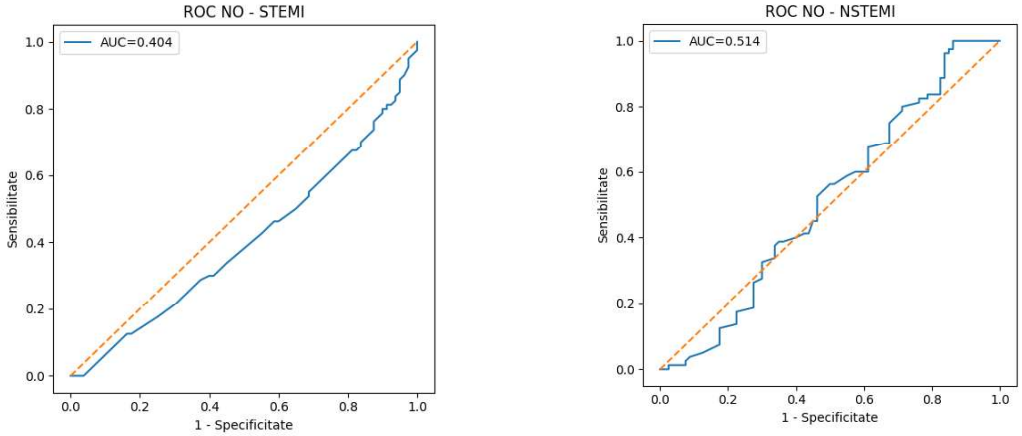


Figure 6. ROC curve for admission NO in STEMI and NSTEMI patients

Endothelial microparticles had modest mortality-prediction performance according to ROC AUC (0.608), and only in STEMI (Figure 7).

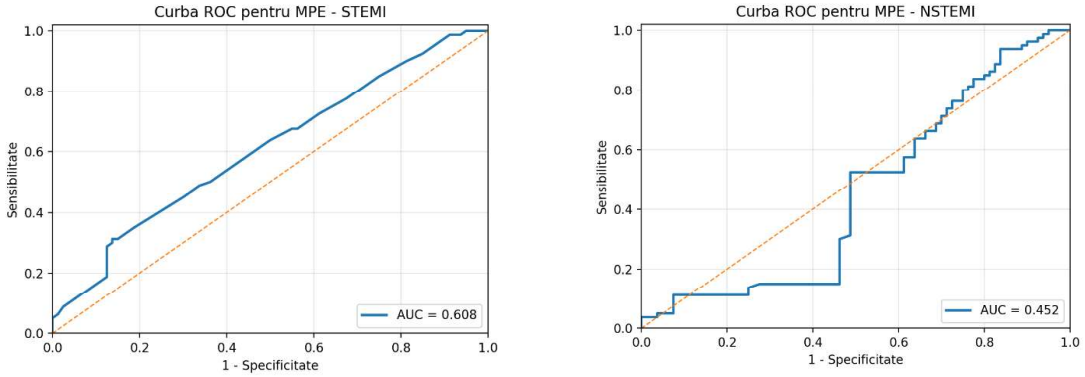


Figure 7. ROC curve for admission endothelial microparticles in STEMI and NSTEMI patients

The optimal Youden-index cutoff was 335.1 particles/mL, yielding sensitivity of 31.2% and specificity of 86.2%. This indicates modest discrimination, with specificity relatively better than sensitivity at the chosen cutoff (Table 33).

Table 33. ROC parameters for endothelial microparticles in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity	Specificity	Youden	Interpretare
STEMI	0.608	335.1	31.2%	86.2%	0.175	Modest prediction
NSTEMI	0.452	208.9	93.8%	16.2%	0.100	Absent/poor prediction

Endocan, a glycoprotein considered an early marker of endothelial dysfunction, showed no predictive value for mortality when measured at admission (Figure 8).

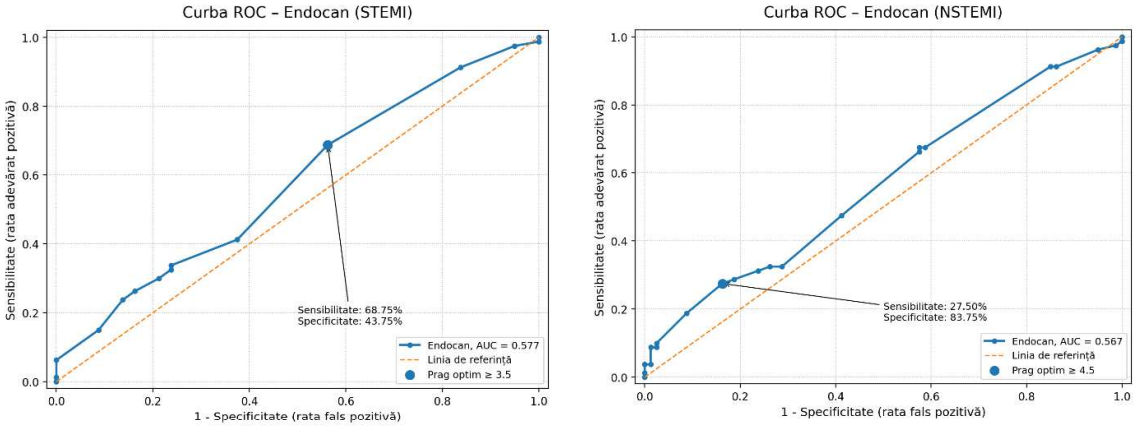


Figure 8. ROC curve for admission endocan in STEMI and NSTEMI patients

Whereas increased endothelial microparticles are considered a sign of severe vascular endothelial injury, endocan may also rise with low-grade, subclinical inflammation. As inflammation subsides on day seven, the difference in endocan levels between nonsurvivors and survivors with STEMI or NSTEMI becomes substantial, suggesting less recovery among nonsurvivors. Endocan measured seven days after angioplasty therefore shows high predictive value for mortality (Figure 9).

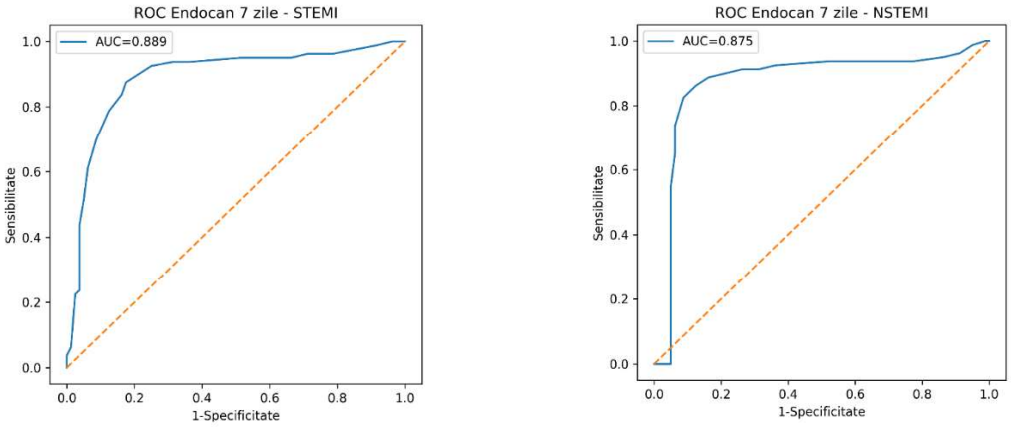


Figure 9. ROC curve for endocan measured on day seven in STEMI and NSTEMI patients

According to AUC, endocan measured during the period of M2 macrophage expression had high to very high predictive power: 0.889 in STEMI and 0.875 in NSTEMI. Sensitivity and specificity exceeded 82.5% in both groups.

Table 34. ROC parameters for endocan seven days after angioplasty in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity	Specificity	Accuracy
STEMI	0.889	≥ 2.40	87.5%	82.5%	85.0%
NSTEMI	0.875	≥ 2.50	86.2%	87.5%	86.9%

Angiopoietin-2 is an important marker of the vascular endothelium's capacity for functional recovery. It limits endothelial progenitor cell activity and promotes endothelial dysfunction. Admission serum angiopoietin-2 was higher in STEMI than in NSTEMI, suggesting greater predictive potential for death in STEMI. Indeed, ROC analysis confirmed a higher predictive value of angiopoietin-2 in STEMI (Figure 10).

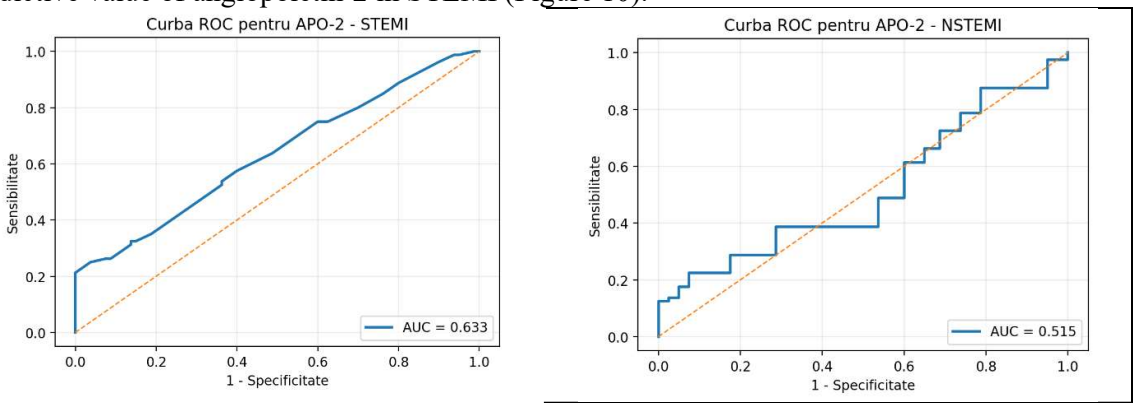


Figure 10. ROC curve for admission angiopoietin-2 in STEMI and NSTEMI patients

In STEMI, angiopoietin-2 showed moderate discrimination for mortality prediction (AUC = 0.633). The optimal cutoff was ≥3666.7 pg/mL, yielding 21.2% sensitivity and 100.0% specificity. In NSTEMI, predictive performance was lower (AUC = 0.515). The calculated cutoff was ≥3574.8 pg/mL, with 22.5% sensitivity and 92.5% specificity (Table 35). Smaller survivor–nonsurvivor differences explain the more modest ROC discrimination.

Table 35. ROC parameters for angiopoietin-2 in STEMI and NSTEMI patients

Group	AUC	Prag APO-2	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden
STEMI	0.633	≥ 3666.7	21.2%	100.0%	100.0%	55.9%	60.6%	0.212
NSTEMI	0.515	≥ 3574.8	22.5%	92.5%	75.0%	54.4%	57.5%	0.150

An amplified inflammatory response against a background of endothelial dysfunction clearly compromises hemostatic control. The von Willebrand factor/ADAMTS13 ratio reflects primary or platelet hemostasis, whereas fibrin monomers are markers of secondary hemostasis and coagulation activation. Platelet microparticles, an emerging hemostasis marker, may activate both primary and secondary hemostasis because of their high platelet-factor content. At admission, the von Willebrand factor/ADAMTS13 ratio was significantly higher than in controls in both groups and was further elevated in nonsurvivors, with moderate predictive potential (Figure 11).

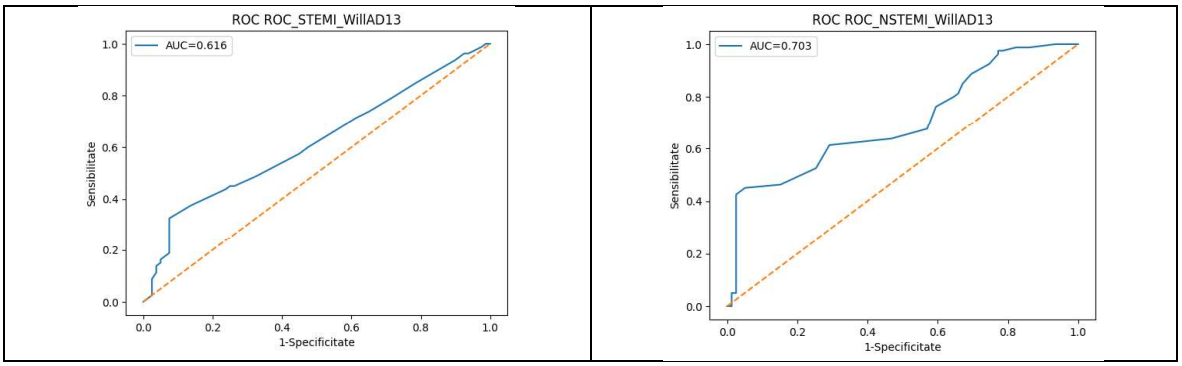


Figure 11. ROC curve for the admission von Willebrand factor/ADAMTS13 ratio in STEMI and NSTEMI patients

This marker predicted mortality in both STEMI and NSTEMI, with better performance, including ROC parameters, in NSTEMI (Table 36).

Table 36. ROC parameters for von Willebrand factor/ADAMTS13 in STEMI and NSTEMI patients

Group	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)	Test direction
STEMI	0.615	2.80	51.3	76.3	Positive
NSTEMI	0.703	2.90	67.5	67.1	Positive

Similar predictive potential was seen for platelet microparticles. Their predictive value was greater in NSTEMI (Figure 12). An AUC of 0.823 indicated good (high to very high) discrimination for mortality prediction. The optimal threshold was 327.60, with 78.8% sensitivity and 88.8% specificity (Table 37).

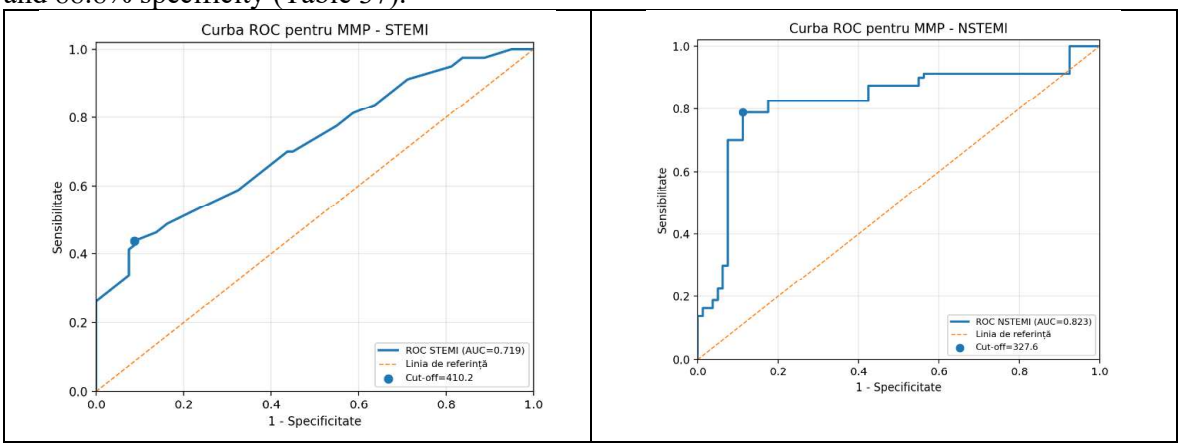


Figure 12. ROC curve for admission platelet microparticles in STEMI and NSTEMI patients

In NSTEMI patients, the AUC reached 0.719, indicating moderately high discrimination by platelet microparticles for mortality prediction. The optimal threshold was 410.20, with 43.8% sensitivity and 91.2% specificity (Table 37).

Table 37. ROC parameters for platelet microparticles in STEMI and NSTEMI patients

Group	AUC	Prag MMP	Sensitivity	Specificity	Youden	Accuracy	Correct classifications
STEMI	0.719	410.20	43.8%	91.2%	0.350	67.5%	108/160
NSTEMI	0.823	327.60	78.8%	88.8%	0.675	83.8%	134/160

Given the similar predictive values of the von Willebrand factor/ADAMTS13 ratio and platelet microparticles, they could be evaluated together, at least to clarify the mechanisms of procoagulant activation in disturbed hemostasis and identify appropriate therapeutic targets. Their

predictive utility is more pronounced in NSTEMI. Fibrin monomers reflect the risk of fibrin thrombus formation through fibrinogen depolymerization by the thrombokinase system, whose enzymatic activation may be closely related to increased platelet microparticles. In STEMI, fibrin monomer levels were higher in nonsurvivors than survivors, with good ROC discrimination (Figure 13), supporting their usefulness as mortality prognostic markers.

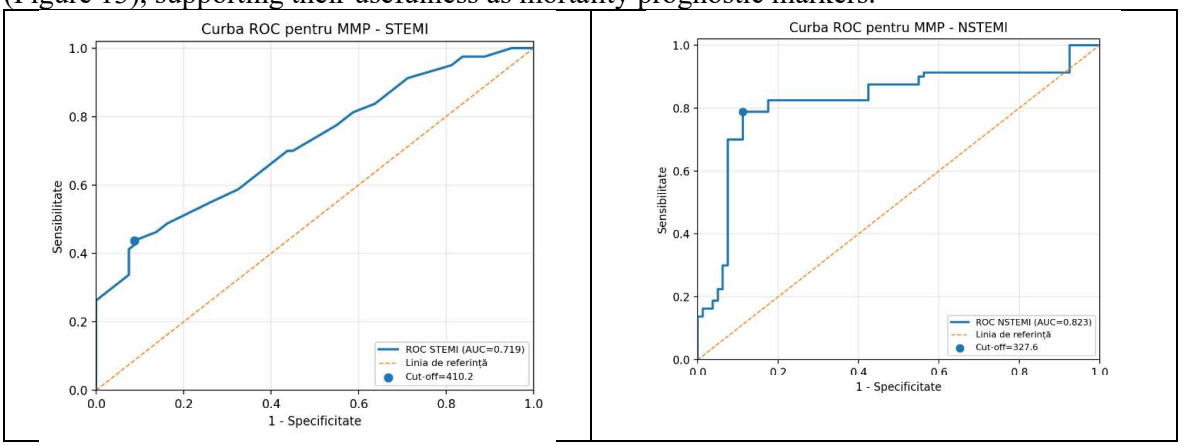


Figure 13. ROC curve for admission fibrin monomers in STEMI and NSTEMI patients

In NSTEMI, the AUC was lower than in STEMI but remained above the nondiscrimination level (AUC = 0.5). Extreme values among NSTEMI survivors increase variability and lower specificity at low cutoffs, which should be considered clinically.

Thus, fibrin monomers have predictive value for mortality in both STEMI and NSTEMI, with more convincing performance in STEMI.

A clinically feasible mortality-prediction algorithm should include a limited number of markers with good predictive performance and pathophysiological relevance to individualized treatment. In this context, growth differentiation factor-15 (GDF-15) is especially important because it integrates inflammation, endothelial dysfunction, oxidative stress and hemostasis. Its ROC curve demonstrates mortality-prediction performance (Figure 14).

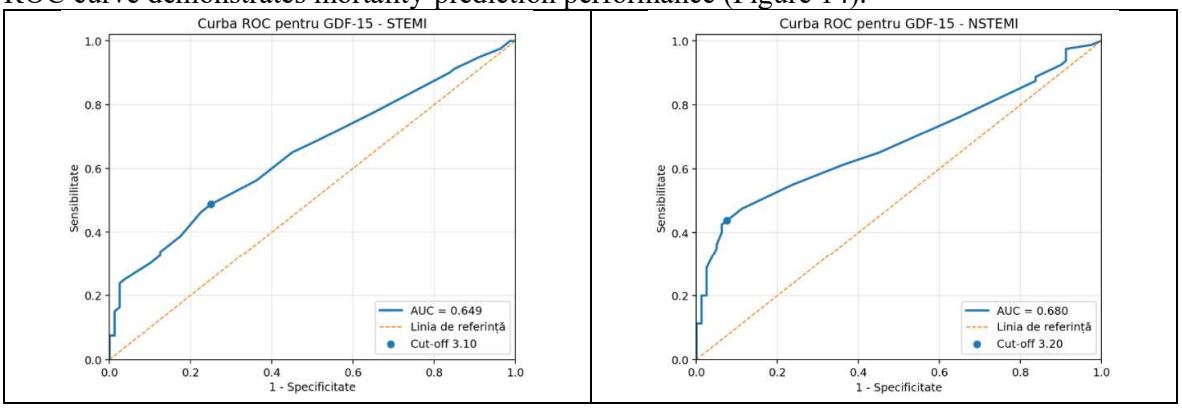


Figure 14. ROC curve for admission GDF-15 in STEMI and NSTEMI patients

In STEMI, the AUC was 0.649 (95% CI 0.562–0.731), compared with 0.680 (95% CI 0.594–0.758) in NSTEMI. Sensitivity was similar in the two groups, whereas specificity was higher in NSTEMI (Table 38).

Table 38. ROC parameters for GDF-15 in STEMI and NSTEMI patients

Group	AUC	AUC 95% CI	Optimal cutoff	Sensitivity	Specificity	Youden
STEMI	0.649	0.562–0.731	3.10	48.8%	75.0%	0.238
NSTEMI	0.680	0.594–0.758	3.20	43.8%	92.5%	0.363

These findings show that GDF-15 predicts mortality in both groups, with comparable performance in STEMI and NSTEMI. Mean GDF-15 levels were also higher in nonsurvivors than survivors in both conditions, supporting its use for mortality-risk prediction. NT-proBNP reflects the quality of cardiac remodeling both before revascularization and during post-infarction recovery, processes fundamentally influenced by the area of myocardial necrosis in STEMI and NSTEMI. Assessment of NT-proBNP revealed substantially greater predictive value in STEMI (Figure 15).

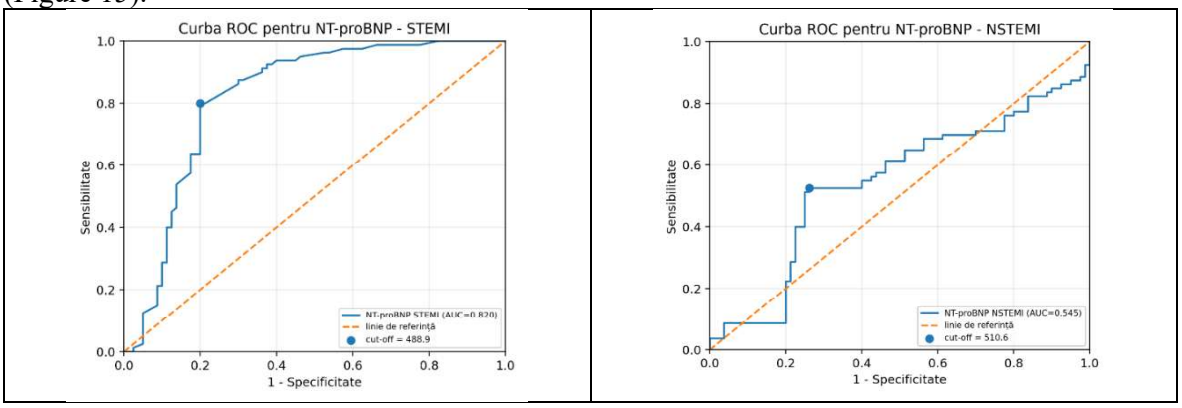


Figure 15. ROC curve for admission NT-proBNP in STEMI and NSTEMI patients

The empirical AUC for NT-proBNP in STEMI was 0.820 (95% CI 0.755–0.886), indicating good discrimination for mortality prediction. The optimal Youden-index cutoff was NT-proBNP ≥488.9 pg/mL, with both sensitivity and specificity of 80.0% (Table 37, as cited in the source).

Table 39. ROC parameters for NT-proBNP in STEMI and NSTEMI patients

Group	AUC	AUC 95% CI	NT-proBNP cutoff	Sensitivity	Specificity	Youden J	p
STEMI	0,820	0,755–0,886	≥ 488,9	80,00%	80,00%	0,600	<0,001
NSTEMI	0,545	0,456–0,634	≤ 510,6	52,50%	73,75%	0,263	0,325

In NSTEMI, the empirical AUC was 0.545 (95% CI 0.456–0.634; p = 0.325), indicating nonsignificant predictive performance close to the reference line. The reverse-direction empirical cutoff was NT-proBNP ≤510.6, with 52.50% sensitivity and 73.75% specificity. Overall, NT-proBNP alone did not adequately distinguish nonsurvivors from survivors in NSTEMI, unlike in STEMI. Elevated NT-proBNP reflects hemodynamic load, ventricular dysfunction and the severity of myocardial injury, consistent with unfavorable progression in STEMI.

5. CLINICAL PROFILE AND ADMISSION MULTIMARKER PANEL IN NONOBSTRUCTIVE CHRONIC CORONARY DISEASE

5.1. Clinical and paraclinical characteristics of noCCD patients

The prospective descriptive observational study conducted at the Institute of Cardiology during 2024–2025 included 171 consecutive patients with confirmed noCCD.

Inclusion criteria:

- age ≥18 years;
- anginal symptoms or ischemic equivalents;
- absence of coronary stenoses ≥50%;
- patient consent to participate.

Exclusion criteria:

- obstructive coronary lesions;
- severe valvular disease;
- advanced cardiomyopathy;
- systemic disease with a poor prognosis;
- refusal to participate.

Diagnostic methods:

Clinical examination, ECG, ambulatory ECG (Holter) monitoring, echocardiography, exercise testing, coronary angiography/coronary CT, and laboratory tests (complete blood count, lipid profile, blood glucose, creatinine and other routine biochemical parameters). The 80-patient group selected for multimarker panel assessment was drawn from the 171-patient cohort with the following demographic and clinical characteristics (Table 40).

Table 40. Demographic characteristics and cardiovascular risk factors in noCCD patients

Risk factor	Prevalence
Age ≥45 years (men) / ≥55 years (women)	71,8%
Arterial hypertension	87,1%
Dislipidemie	83,0%
Diabetes mellitus	22,8%
Overweight/obesity	68,9%
Central obesity	38,0%
Current/former smokers	16,4%
Sedentary lifestyle	34,3%

Key observations from the cohort analysis:

♦ This study confirms that noCCD within the INOCA spectrum is a common clinical entity with distinct demographic and clinical features. The predominance of women (63.7%) and a mean age above 60 years are consistent with international literature describing INOCA as particularly common among postmenopausal women with increased coronary microvascular vulnerability.

♦ The cardiovascular risk profile—dominated by arterial hypertension (87.1%), dyslipidemia (83.0%), obesity (68.9%) and diabetes mellitus (22.8%)—suggests a substantial metabolic burden, consistent with pathophysiological mechanisms of endothelial and microvascular dysfunction. Chronic low-grade inflammation, insulin resistance and autonomic dysfunction are known contributors to microvascular disease, even in the absence of significant epicardial lesions. These findings agree with recent studies (WISE, CorMicA and the EAPCI Consensus), which emphasize the link between metabolic syndrome and microvascular ischemia.

♦ Anginal symptoms predominate clinically, with most patients reporting typical anginal pain, often precipitated by exertion or emotional stress. One-quarter reported pain at rest; morning episodes suggest a vasomotor or microvascular origin of ischemia, a core feature of noCCD. Weather sensitivity and stress-related pain also suggest autonomic involvement.

♦ A notable paraclinical finding was preserved systolic function (mean ejection fraction ≥50% in 95.3% of patients) despite diastolic dysfunction in 50%. This dissociation, reported in numerous studies, reflects concentric remodeling, myocardial stiffness and altered [sentence incomplete in the original].

♦ Coronary investigations were consistent with noCCD: more than 60% of patients had no epicardial lesions, while the remainder had nonobstructive plaques only (less than 50%). Coronary CT showed similar findings, suggesting minimal epicardial atherosclerosis without excluding substantial microvascular disease. Functional tests (ECG, Holter monitoring and exercise testing) showed heterogeneous, mild ischemic changes, reflecting intermittent nonobstructive microvascular ischemia. Normal functional tests in a small subset did not exclude the diagnosis, because coronary flow reserve may be impaired without obvious ECG changes.

♦ The treatment profile showed good implementation of ESC secondary-prevention recommendations, with high and stable use of statins, beta-blockers and renin–angiotensin system inhibitors throughout the year. Frequent use of trimetazidine reflects current interest in metabolic treatment for microvascular angina, with reported benefits for symptom reduction and exercise tolerance.

5.2. Multimarker panel assessment in patients with nonobstructive chronic coronary disease

The principal inflammatory markers are presented in Table 41.

Table 41. Circulating inflammatory marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	p
IL-1β (pg/ml)	5,13±0,68 Mediana: 5,15	7,45±1,18 Mediana: 7,6	+45,2%	<0,001
IL-6 (pg/ml)	4,36±0,64 Mediana: 4,38	4,53±1,75 Mediana: 4,15	+3,9%	=0,241
R-IL-6 (pg/ml)	1,24±0,35 Mediana: 1,3	2,34±0,7 Mediana: 2,4	+88,7%	<0,001
IL-10 (pg/ml)	7,77±0,98 Mediana: 7,55	7,35±1,8 Mediana: 7,55	-5,4%	=0,0529
hsCRP (mg/L)	1,45±0,41 Mediana: 1,42	3,93±1,39 Mediana: 4,35	+171%	<0,001
TNF-α (pg/ml)	5,85±0,92 Mediana: 5,75	6,28±1,44 Mediana: 7,0	+7,4%	=0,024
Neopterin (nM/L)	3,48±0,72 Mediana: 3,49	3,72±0,95 Mediana: 3,6	+6,9%	=0,0547
Neopterin (nM/L) *	3,48±0,72 Mediana: 3,49	5,16±0,58 Mediana: 5,23	+48,3%	<0,001

Legend: Neopterin was measured among patients in whom AAETAR was detected (n = 16); ±% indicates the relative deviation of marker levels in noCCD from controls; p indicates statistical significance compared with controls.

The findings indicate an intensified inflammatory response in nonobstructive chronic coronary disease, consistent with a mean hsCRP level greater than 3 (3.93 ± 1.39 mg/mL), which according to AHA/ACC/ESC consensus indicates high cardiovascular risk. Serum IL-1β, a primary inflammatory marker, was 45.2% higher than in controls. Regardless of the noninfectious triggers of inflammation, IL-1β is the first marker expressed by cells exposed to damage-associated molecular patterns (DAMPs) and is considered a useful indicator of inflammatory activity. The CANTOS trial demonstrated the efficacy of the IL-1β inhibitor canakinumab in patients with previous myocardial infarction and elevated hsCRP and TNF-α. However, IL-6 increased nonsignificantly, whereas its soluble receptor (sIL-6R) was 88.7% higher than in controls. Notably, IL-1β and soluble IL-6 receptor were the markers identified as mortality predictors in STEMI and NSTEMI. The classical proinflammatory marker TNF-α increased by only 7.5% relative to controls, although this increment was significant. The range of inflammatory markers continues to expand as new evidence emerges; neopterin is noteworthy because it also reflects immune inflammation. It was therefore of interest among patients with circulating agonistic autoantibodies to ET-1 ETA receptors (AAETAR), associated with various autoimmune disorders. In our overall cohort, neopterin increased by a nonsignificant 6.9% (p = 0.0547), but in the 16 patients with different AAETAR titers it was 48.3% above control levels, a significant increase.

Neopterin may thus be an important CMD predictor in patients with autoimmune diseases (e.g., rheumatoid arthritis, scleroderma and psoriasis), reflecting the degree of macrophage activation. CMD occurs more frequently in autoimmune rheumatic disease, where the myocardial perfusion reserve index is reduced. The moderate inflammatory activation in noCCD may partly reflect preserved expression of IL-10, an anti-inflammatory marker that limits the inflammatory response by suppressing proinflammatory markers. IL-10 was reduced by only 5.4%, nonsignificantly (p = 0.0529). According to the principal markers, endothelial dysfunction in noCCD was less pronounced than in STEMI or NSTEMI (Table 42).

Table 42. Circulating endothelial dysfunction marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	P
MPE (CD144+) (count/mL)	145,58±10,46 Mediana: 148,39	158,44±55,69 Mediana: 133,25	+8,8%	=0,0892
Endocan (ng/ml)	1,27±0,41 Mediana: 1,3	1,52±0,57 Mediana: 1,5	+19,7%	=0,002
NO (μM/L)	74,21±8,47 Mediana: 73,1	63,75±14,77 Mediana: 63,7	-14,1%	<0,001
Apo-2 (pg/ml)	2146,07±122,94 Mediana: 2149	2719,64±396,71 Mediana: 2848,95	+27,4%	<0,001
CPE (count/μL)	499,15±63,40 Mediana: 492,45	472,12±117,36 Mediana: 491,95	-5,4%	=0,0543

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

Circulating endothelial microparticles, a new marker of endothelial cell injury, did not differ significantly from controls, increasing by only 8.8% (p = 0.0892). Endocan, a glycoprotein of the endothelial glycocalyx that undergoes cleavage under the action of factors such as oxygen and nitrogen free radicals, proinflammatory cytokines and advanced glycation end-products (AGEs), was nevertheless 19.7% higher (p = 0.002). This increase was associated with a 14.1% decline in nitric oxide (p < 0.001), which may represent a crucial mechanism underlying disturbed coronary microcirculation. Endothelial injury and dysfunction are reversible processes, both during favorable natural progression and with adequate effective treatment. Circulating endothelial progenitor cells did not decline significantly from control levels (a 5.4% reduction; p = 0.0543). Nevertheless, their endothelial repair potential was diminished by a significant 27.4% increase in angiopoietin-2. Angiopoietin-2 compromises endothelial progenitor cell incorporation at sites of injury, thereby impairing re-endothelialization and maintaining reduced NO availability. This adversely affects coronary microvascular reactivity, reflected in a myocardial coronary flow reserve below 2, the principal pathophysiological criterion for CMD. Inflammation and endothelial dysfunction are major pathophysiological contributors to NETosis, a phenomenon clearly documented in ACS by significantly elevated circulating specific markers. NETosis activates oxidative stress and releases proteases that cleave the extracellular matrix and initiate apoptosis in myocardial cells and coronary vessel walls. Among the noCCD patients in our study, NETosis markers were increased relative to controls, but not significantly (Table 43).

Table 43. Circulating NETosis marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	P
MMP-8 (ng/ml)	28,81±6,45 Mediana: 28,7	30,78±9,08 Mediana: 30,55	+8,8%	=0,0767
Elastase (ng/ml)	16,16±4,14 Mediana: 15,8	17,63±6,09 Mediana: 15,6	+9,1%	=0,0553
MPO (U/ml)	29,25±5,87 Mediana: 28,9	31,34±9,2 Mediana: 31,7	+7,1%	=0,0624
E-selectin (ng/ml)	64,36±7,93 Mediana: 63,65	71,14±11,73 Mediana: 63,55	+10,5%	=0,0791

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

MMP-8 increased by 8.8%, neutrophil elastase by 9.1%, myeloperoxidase by 7.1% and E-selectin by 10.5%. The limited expression of E-selectin is consistent with normal IL-10 and endothelial microparticle levels. Inflammation and endothelial dysfunction are central to the microspastic mechanism of CMD and noCCD. They may also strongly influence diffuse microthrombosis, whose assessment and prediction require hemostasis marker analysis (Table 44).

Table 44. Circulating hemostasis marker levels in patients with nonobstructive chronic coronary disease

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	P
MF (mg/ml)	4,54±0,63 Mediana: 4,4	4,75±0,94 Mediana: 4,78	+4,6%	=0,0716
MPP, CD62P (1/µL)	161,37±16,85 Mediana: 158,8	175,46±67,77 Mediana: 148,3	+8,7%	=0,059
von Willebrand factor/ AMDATS13 (arbitrary units)	1,26±0,38 Mediana: 1,3	1,89±0,59 Mediana: 1,8	+50%	<0,001

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

Unlike in ACS, the coagulation state associated with secondary hemostasis was not activated in noCCD, as indicated by the nonsignificant 4.6% increase in fibrin monomers relative to controls ($p = 0.0716$). Circulating platelet microvesicles or microparticles were likewise only nonsignificantly elevated by 8.7% ($p = 0.059$), suggesting that the associated mechanism of primary or platelet hemostasis activation was not markedly impaired. Nevertheless, platelet hemostatic regulation was disturbed in noCCD, as shown by a significant 50% increase in the von Willebrand factor/ADAMTS13 ratio, suggesting impaired endogenous downregulation of von Willebrand factor activity. Increased circulating von Willebrand factor correlates directly with higher endocan, since cleavage of the endothelial glycocalyx is associated with von Willebrand factor release from Weibel–Palade bodies, initiating platelet adhesion to subendothelial collagen receptors. The von Willebrand factor/ADAMTS13 ratio is therefore useful for investigating the microthrombotic mechanism of CMD and noCCD. The microvasospastic mechanism develops against a background of endothelial dysfunction but may also arise from neuroendocrine activation

and excessive accumulation of vasoconstrictor mediators. We therefore measured the circulating levels of relevant factors (Table 45).

Table 45. Circulating neuroendocrine activity marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	P
Neprilysin (ng/ml)	0,49±0,38 Mediana: 0,34	0,94±0,36 Mediana: 0,9	+91,8%	<0,001
Ang1-7/Ang II (arbitrary units)	0,88±0,064 Mediana: 0,88	0,69±0,55 Mediana: 0,5	-21,6%	=0,0053
AAETAR (ng/dL)	0 Mediana: —	4,84±0,8 (n=16) Mediana: 4,29	—	<0,001
Adrenomedullin (pg/ml)	12,82±2,99 Mediana: 12,94	20,55±4,68 Mediana: 20,21	+60,3%	<0,001
NT-proBNP (pg/ml)	142,44±17,25 Mediana: 142,88	151,23±45,16 Mediana: 152,17	+6,4%	>0,05
Catestatin (ng/ml)	1,75±0,34 Mediana: 1,77	0,85±0,27 Mediana: 0,87	-51,5%	<0,001

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

Neprilysin levels were almost twice those in controls (+91.8%). This finding is conceptually significant, including in light of the known benefits of the neprilysin inhibitor sacubitril in disturbances of circulatory homeostasis. In noCCD, the Ang 1–7/Ang II ratio was significantly reduced by 21.6% (p = 0.0053), largely because of reduced Ang 1–7, potentially explained by excess neprilysin. A novel finding was the presence of AAETAR in 16 noCCD patients, with a mean circulating level of 4.84 ± 0.8 ng/dL. Most of these patients (14 of 16, 87.5%) had autoimmune conditions involving rheumatoid arthritis or psoriasis. Sympathoadrenergic activation represents another dimension of neuroendocrine involvement in CMD and noCCD. Supporting this mechanism is the significant 51.5% reduction in catestatin, an oligopeptide that inhibits central sympathetic activation at the ventrolateral medullary nuclei. Thus, a reduced Ang 1–7/Ang II ratio and sympathetic activation support important microvasospastic mechanisms in CMD and noCCD. Regardless of the prevailing pathophysiological endotype, noCCD progression involves coronary and myocardial remodeling occurring alongside atherosclerosis, whose markers may be predictors of CMD (Table 46).

Table 46. Circulating cardiovascular remodeling marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	P
GDF-15 (ng/mL)	1,29±0,44 Mediana: 1,4	2,45±0,75 Mediana: 2,5	+89,9%	<0,001
FGF-21 (pg/ml)	64,29±6,39 Mediana: 63,9	66,36±8,09 Mediana: 65,4	+3,2%	=0,0532
TGF-1β (ng/ml)	4,85±0,87 Mediana: 4,7	5,11±1,36 Mediana: 4,7	+5.4%	=0,1
Syndecan-1 (ng/ml)	125,86±7,39 Mediana: 125,9	128,25±15,81 Mediana: 124,6	+1,9%	=0,0601
Galectin-3 (ng/ml)	3,52±0,78 Mediana: 3,51	3,81±1,28 Mediana: 3,55	+8,2%	=0,05789
MMP-2 (ng/ml)	2,95±0,77 Mediana: 2,85	3,81±1,28 Mediana: 3,4	+8,2%	=0,0511
MMP-9 (ng/ml)	14,71±2,64 Mediana: 14,65	16,35±7,87 Mediana: 13,45	+11,1%	=0,0614

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

Unlike in ACS, the markers assessed in noCCD did not show promising diagnostic value, except for GDF-15. The pathophysiological significance of GDF-15 in CMD remains insufficiently clarified and requires further evidence. Our interest was prompted by studies describing GDF-15 as a CMD predictor in STEMI, a finding also supported by our research, including its ability to predict death. The classical concept of noCCD appropriately emphasizes the central role of atherosclerosis, although epicardial stenoses often remain below 50% even in older patients. Changes in reliable atherogenicity and oxidative stress markers, which interact reciprocally with inflammation, are therefore important (Table 47).

Table 47. Circulating oxidative stress and atherogenicity marker levels in patients with noCCD

Marker	Control (n=60) mean ± SD and median	noCCD (n=80) mean ± SD and median	±%	p
NOX-2 (pg/ml)	21,64±4,54 Mediana: 21,15	28,93±8,36 Mediana: 30,5	+33,7%	<0,001
MDA (µmol/L)	4,42±0,64 Mediana: 4,4	4,82±1,28 Mediana: 4,8	+9,05%	=0,0136
AOPP (µmol/L)	41,83±4,53 Mediana: 40,8	50,26±7,15 Mediana: 49,7	+20.2%	<0,001
Paraoxonase-1 (nM/mL)	421,55±25,14 Mediana: 419,85	314,32±52,38 Mediana: 316,8	-25,4%	<0,001
Oxidized HDL (arbitrary units)	1±0,15 Mediana: 1	2,47±0,9 Mediana: 2,46	+147%	<0,001

Legend: ±% – relative marker changes in noCCD versus controls; p – significance versus controls.

The results indicate activation of oxidative stress in noCCD, evidenced by a significant 33.7% increase in serum NOX2 and increases in principal lipid and protein peroxidation products: malondialdehyde by 9.05% and advanced oxidation protein products by 20.2%. Oxidative stress may explain reduced nitric oxide, because premature NO metabolism results from its reaction with superoxide anions, forming peroxynitrite, a vasoconstrictor and cytotoxic product that induces inflammation, apoptosis, and cellular migration and proliferation. Assessment of atherogenicity has evolved with the identification of new useful markers, from lipid-profile indices and endothelial dysfunction markers to paraoxonase-1, oxidized LDL and oxidized HDL.

We measured paraoxonase-1 and oxidized HDL, markers reflecting cholesterol removal from the subintimal area. Paraoxonase-1 attenuates oxidation of HDL molecules, improving cholesterol removal. Oxidized HDL was substantially elevated, 147% above controls, associated with a significant 25.4% reduction in paraoxonase-1. Accordingly, paraoxonase-1 may serve as a meaningful marker of active atherosclerosis and a therapeutic target.

SUMMARY OF RESULTS

The study found similar 12-month mortality rates in STEMI and NSTEMI (16.3% and 15.5%, respectively). A plausible explanation is more severe reperfusion injury in NSTEMI, reflected by greater increases in H-FABP, consistent with the Heusch concept and supporting the assessment of changes in H-FABP from admission to 24 hours. The pathophysiological basis may involve intensified NETosis and inflammation, providing a rationale for investigating pharmacological suppression of these processes during reperfusion. Patients with STEMI and NSTEMI showed broadly similar preprocedural marker changes relative to controls, while significant differences between nonsurvivors and survivors were common to both conditions. The inflammatory response in nonsurvivors was characterized by elevated IL-1β and soluble IL-6 receptor, consistent with studies linking these markers to adverse STEMI and NSTEMI outcomes [15, 16]. Increased neopterin reflects immune-system involvement, and its association with RNase activity highlights the potential role of microRNA families [17]. Endocan and angiopoietin-2, novel markers of endothelial dysfunction, were significantly more elevated in nonsurvivors than survivors with STEMI and NSTEMI, as reported in other investigations of their predictive value in ACS [18, 19]. Higher platelet microparticles and von Willebrand factor/ADAMTS13 ratios, as well as GDF-15 and FGF-21, suggest contributions from prothrombotic mechanisms and cardiovascular remodeling, while NT-proBNP was elevated only in STEMI nonsurvivors. The Ang 1–7/Ang II ratio, a new neuroendocrine activity indicator, was significantly reduced in nonsurvivors with either infarction type. Markers with high or very high predictive power at admission according to ROC AUC (0.823–0.932) were IL-1β, soluble IL-6 receptor, platelet microparticles and NT-proBNP. Endocan showed high predictive value for mortality in both STEMI and NSTEMI when measured on day seven after angioplasty. Multimarker assessment in noCCD sought CMD diagnostic markers using three main considerations: (1) maximal deviations from controls; (2) comparison with the corresponding markers in STEMI and NSTEMI on day seven after angioplasty; and (3) recognition that myocardial revascularization does not eliminate CMD, which may precede angioplasty or be caused by it. Relevant markers included IL-1β, soluble IL-6 receptor, angiopoietin-2, NO, endothelial progenitor cells, Ang 1–7/Ang II, platelet microparticles, von Willebrand factor/ADAMTS13 and GDF-15. Because angiopoietin-2 reflects coronary arteriolar stiffness and resistance—a determinant of the key diagnostic CMD index—as well as capillary rarefaction and impaired coronary vasodilator and vasoconstrictor reactivity [20], it may be investigated as an alternative to NO, endothelial progenitor cells and Ang 1–7/Ang II. Thus six markers—IL-1β, soluble IL-6 receptor, angiopoietin-2, platelet microparticles, von Willebrand factor/ADAMTS13 and GDF-15—may form a CMD diagnostic algorithm and guide individualized treatment targeting the underlying mechanisms. The potential diagnostic relevance of GDF-15 in noCCD is consistent with its role in CMD in STEMI reported by other authors [21, 22] and with evidence of its long-term mortality prognostic value in ACS [23].

GENERAL CONCLUSIONS

1. Twelve-month mortality after angioplasty was comparable among 558 STEMI and 614 NSTEMI patients, at 16.3% and 15.5%, respectively. During hospitalization (five to seven days on average), mortality was substantially higher in STEMI than NSTEMI: 7.3% versus 3.3%.
2. The admission multimarker panel revealed significant deviations from controls for all 44 markers in both STEMI and NSTEMI. Markers significantly differing between nonsurvivors and survivors included IL-1β (+25.4%), soluble IL-6 receptor (+51.1%), NO (−6%), angiopoietin-2 (+8.7%), platelet microparticles (+40.8%), von Willebrand factor/ADAMTS13 (+35.9%), Ang 1–7/Ang II (−20.9%), GDF-15 (+43%) and FGF-21 (+7.3%), indicating contributions from inflammation, endothelial and hemostatic dysfunction, neuroendocrine activation and myocardial remodeling. STEMI nonsurvivors additionally showed significantly increased NT-proBNP (45%), endothelial microparticles and E-selectin (8.6%). In NSTEMI nonsurvivors, endocan (+11.2%) and paraoxonase-1 (−7.6%) were particularly notable.
3. A novel neuroendocrine marker, AAETA (agonistic autoantibody against the ET-1 type A receptor), which induces vasoconstriction and coronary constriction similar to ET-1, was detected at admission in 20 deceased STEMI patients and 16 deceased NSTEMI patients, at mean levels of 3.53–3.64 ng/dL. AAETA was not detected in any STEMI or NSTEMI survivor. Its presence may therefore predict 12-month mortality among ACS patients with associated autoimmune disorders.
4. Odds-ratio analysis identified eight markers common to STEMI and NSTEMI with mortality odds ratios greater than 2: IL-1β, soluble IL-6 receptor, angiopoietin-2, platelet microparticles, von Willebrand factor/ADAMTS13, Ang 1–7/Ang II, GDF-15 and FGF-21. ROC AUC analysis demonstrated excellent mortality-prediction performance in STEMI for IL-1β (AUC = 0.914; cutoff >7.9 pg/mL) and NT-proBNP (AUC = 0.820; cutoff >488.9 pg/mL). In NSTEMI, soluble IL-6 receptor (AUC = 0.932; cutoff >3.3 pg/mL) and platelet microparticles (AUC = 0.823; cutoff >327.6 CD62P, 1/μL) showed particularly strong performance. Endocan measured on day seven showed similarly high predictive power in STEMI (AUC = 0.889; cutoff >2.4 ng/mL) and NSTEMI (AUC = 0.875; cutoff >2.5 ng/mL).
5. Assessment of myocardial injury during reperfusion (24 hours versus admission) revealed significantly larger increases in H-FABP and ischemia-modified albumin in nonsurvivors than survivors: in STEMI by 102.3% and 66.7%, respectively, and in NSTEMI by 114% and 120%, respectively. NSTEMI nonsurvivors also showed greater increases than STEMI nonsurvivors—22.3% for H-FABP and 35.4% for ischemia-modified albumin—supporting the Heusch concept established in basic research of an inverse association between myocardial reperfusion tolerance and ischemic preconditioning. Greater reperfusion injury in NSTEMI was accompanied by more marked inflammation, endothelial dysfunction, hemostatic disturbance and NETosis, as shown by changes in IL-1β, platelet and endothelial microparticles, endocan, elastase, MMP-8, myeloperoxidase and GDF-15.
6. By day seven after angioplasty, the investigated pathogenetic processes improved in all groups, particularly among STEMI and NSTEMI survivors. At the onset of post-infarction myocardial remodeling, patients who subsequently died showed statistically significant adverse changes relative to survivors in key markers of inflammation (IL-1β, soluble IL-6 receptor, IL-10), endothelial dysfunction (endocan and NO), hemostasis (von Willebrand factor/ADAMTS13), NETosis (elastase) and myocardial remodeling (GDF-15 and MMP-9). Most of these markers had admission odds ratios greater than 2, and IL-1β, soluble IL-6 receptor and endocan were also among those with high or very high ROC AUC-based mortality-prediction performance.
7. Multimarker assessment in noCCD identified significant deviations from controls in markers that mostly also predicted mortality in STEMI and NSTEMI: IL-1β, soluble IL-6 receptor, endocan, angiopoietin-2, NO, endothelial progenitor cells, platelet microparticles, von Willebrand factor/ADAMTS13, Ang 1–7/Ang II and GDF-15. These markers may be investigated for CMD diagnosis because they reflect mechanisms of its pathophysiological endotypes. Angiopoietin-2

reflects coronary arteriolar stiffness, which increases resistance, and may integrate or replace endocan, NO, endothelial progenitor cells and Ang 1–7/Ang II. The proposed CMD diagnostic algorithm therefore comprises six markers: IL-1β, soluble IL-6 receptor, angiopoietin-2, platelet microparticles, von Willebrand factor/ADAMTS13 and GDF-15. noCCD was also associated with notable atherogenicity, shown by a 147% rise in oxidized HDL against a 25.4% decrease in paraoxonase-1.

8. The proposed algorithms for predicting 12-month mortality in STEMI and NSTEMI and CMD in noCCD share several markers. The mortality panel is ordered as IL-1β, soluble IL-6 receptor, endocan, platelet microparticles and NT-proBNP; for CMD, the list is supplemented with von Willebrand factor/ADAMTS13, angiopoietin-2 and GDF-15. Potential contributions to individualized treatment include investigation of IL-1β and IL-6 receptor blockade and improvements in endothelial and hemostatic dysfunction. NETosis also contributes to the extent of irreversible cardiomyocyte injury during reperfusion. Whether colchicine can reduce this injury and the optimal timing of its administration after revascularization require separate clinical investigation.

PRACTICAL RECOMMENDATIONS

1. For predicting mortality one year after angioplasty, admission IL-1β (>7.9 pg/mL) had superior predictive power in STEMI (AUC = 0.914), whereas soluble IL-6 receptor (>3.3 pg/mL) had very high predictive power in NSTEMI (AUC = 0.932). High hsCRP levels (7.8–8.2 mg/L) reflect inflammatory activity but have limited predictive power for mortality. IL-1β and IL-6 receptor inhibitors or antagonists merit investigation as potential components of optimized individualized post-infarction treatment.

2. Admission serum NT-proBNP can be used as a marker with high predictive value for mortality (AUC = 0.820) in STEMI only.

3. Endocan, a novel endothelial dysfunction marker, can be used as a high-value predictor of mortality in STEMI and NSTEMI (AUC = 0.889 and 0.875, respectively) when measured seven days after angioplasty.

4. H-FABP (heart-type fatty acid-binding protein), a novel marker of cardiomyocyte injury, can be used to predict myocardial reperfusion injury in the context of the Heusch phenomenon by measuring its relative increase from admission to 24 hours after angioplasty in both STEMI and NSTEMI. An increase greater than 85% was observed among STEMI nonsurvivors, while a greater than twofold increase characterized NSTEMI nonsurvivors.

5. The multimarker panel used to investigate CMD and its pathophysiological phenotypes in noCCD includes (i) increased angiopoietin-2 and GDF-15 as markers of coronary arteriolar remodeling, stiffness and resistance; (ii) elevated platelet microparticles and the von Willebrand factor/ADAMTS13 ratio as indicators of an activated prothrombotic state; and (iii) increased IL-1β and soluble IL-6 receptor as markers of inflammation.

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LIST OF PUBLICATIONS RELATED TO THE THESIS

1. Single-author monograph

1.1. Munteanu M. Predictive and pathophysiological features of the multimarker panel in patients with acute and nonobstructive chronic coronary syndromes. Tipografia Blitz Poligraf. 2026, p.280

2. Articles in international scientific journals

2.1. Articles in journals indexed in Web of Science, Scopus and other international databases recognized by ANACEC

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3. Articles in accredited national scientific journals

3.1. Articles in category B+ journals

3.1.1. Popovici M., Ciobanu L., Popovici I., Ivanov V., Munteanu M., et al. Features of hemostasis in patients with non-ST-elevation myocardial infarction. Moldovan Medical Journal, 2022, 65(1): 40–47. ISSN 2537-6373 (Print), ISSN 2537-6381 (Online). Category B+ https://ibn.idsi.md/vizualizare_articol/162864

3.2. Articles in category B journals

3.2.1. Dicusar O., Darii O., Popovici I., Munteanu M., et al. The role of cardiac MRI in assessing coronary microvascular dysfunction and identifying other causes of MINOCA in NSTEMI patients. Buletinul Academiei de Științe a Moldovei. Științe medicale, 2022, 1(72): 11–17. ISSN 1857-0011. Category B https://ibn.idsi.md/vizualizare_articol/153732

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4. Invention patents, registration certificates and materials presented at invention exhibitions

4.1. Materials presented at international invention exhibitions

4.1.1. Moscalu V., Popovici M., Munteanu M, et al., The circulating endothelial progenitor cells-a predictor of coronary microcirculation disorder and major advers cardiovascular events (MACE) in patients with acute myocardial infarction without ST segment elevation, 49th International Exhibition of Inventions of Geneva (April 2024)
4.1.2. Munteanu M, Moscalu V., Ciobanu L., et al., SR-Co-ATPose circulonte: un indicoteur de la lesion due myocordique due a la reperfusion et du risque de mortalite apres une angioplostie coronaire, Geneva, April 2025 (Gold medal)

5. Poster presentations at scientific forums

5.1. International forums

5.1.1. Popovici M., Munteanu M., et al. Ang 1–7 improves myocardial tolerance to ischemia and reperfusion impaired by thapsigargin. Romanian Journal of Cardiology, Supplement, 2022, Vol. 32, pp. 208–209
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5.1.14. Sîrbu A., Munteanu M., Popovici I., Popovici M., Ivanov V., Lucia C., Cobeț V. Multimarker phenotypes of nonobstructive chronic coronary disease: integrating inflammation, endothelial dysfunction and primary hemostasis. Romanian Journal of Cardiology. Supplement 2026 2026; 36(Suppl):79-80. (65th National Congress of Cardiology, 16–19 September 2026, Sinaia, Romania; poster).
5.1.15. Munteanu M., Cobeț V., Popovici I.I., Ciobanu L., Popovici I., Ivanov V., Popovici M. Common changes of biomarkers in acute and chronic coronary syndromes: an anchored glance on pathophysiology as well as coronary microcirculation disorder prediction. European Heart Journal, Volume 47, Issue Supplement_1, October 2026, ehag785.1843 https://doi.org/10.1093/eurheartj/ehag785.1843 (ESC Congress 2026, 28–31 August 2026, Munich, Germany; poster).
5.1.16. Munteanu M., Cobeț V., Popovici I.I., Ciobanu L., Popovici I., Ivanov V., Popovici M. Effects of Ang 1-7, taurine and glutamine in the recovery of myocardial dysfunction after transient ischaemia. European Heart Journal, Volume 47, Issue Supplement_1, October 2026, ehag785.1761, https://doi.org/10.1093/eurheartj/ehag785.1761 (ESC Congress 2026, 28–31 August 2026, Munich, Germany; poster).

ANNOTATION

Mihaela Munteanu. Evaluation of Markers of Coronary Microcirculatory Dysfunction in Patients with STEMI, NSTEMI and Nonobstructive Chronic Coronary Disease, and Predictors of Death. Habilitation Thesis in Medical Sciences, Chișinău, 2026.

Thesis structure: The thesis comprises an Introduction, Literature Review, Materials and Methods, three chapters presenting original research results, Discussion, General Conclusions, Practical Recommendations, a bibliography of 226 references, 13 annexes, 267 pages, 27 figures and 101 tables. The research results were published in 48 scientific works.

Keywords: STEMI, NSTEMI, non-obstructive coronary artery disease (CAD), multimarker panel, mortality prediction algorithm, diagnostic markers of coronary microcirculatory dysfunction.

Research aim: To evaluate a multimarker panel in patients with STEMI, NSTEMI, and nonobstructive CAD (BCCno) to identify markers with high predictive value for mortality at 12 months, assess the severity of myocardial reperfusion injury, and identify feasible markers for diagnosing coronary microcirculatory dysfunction.

Research objectives: to determine the 12-month mortality rate among patients with STEMI and NSTEMI; to evaluate the characteristics of the multimarker panel at admission in patients with STEMI and NSTEMI (non-survivors versus survivors); to identify markers with high predictive value for mortality risk based on the area under the receiver operating characteristic curve (ROC AUC); to estimate the severity of myocardial reperfusion injury based on changes in H-FABP during the acute phase of infarction (admission to 24 hours) in patients with STEMI and NSTEMI, in the context of G. Heusch's concept; to evaluate the characteristics of the multimarker panel during the period associated with M2 macrophage expression (day 7) in non-survivors and survivors; to identify markers with plausible diagnostic value for coronary microcirculatory dysfunction in patients with BCCno.

Scientific novelty and originality: the use of a multimarker panel for the combined assessment of established and novel markers reflecting the main pathogenetic mechanisms underlying disrupted circulatory homeostasis, with the aim of developing algorithms to predict mortality and CMD; broadening the application of novel markers to identify pathophysiological features specific to CMD endotypes; the use of H-FABP to assess the validity of Heusch's concept, extrapolated to patients with STEMI and NSTEMI, regarding myocardial injury severity in relation to ischemic preconditioning.

The important scientific problem addressed in this field. Application of the multimarker panel identified markers with plausible diagnostic value for coronary microcirculatory dysfunction in BCCno, as well as markers with high predictive power for mortality risk in patients with STEMI and NSTEMI at 12 months after revascularization, enabling the identification of key pathophysiological features and optimization of individualized treatment.

Theoretical significance: Novel evidence is provided regarding the contribution of inflammation, endothelial dysfunction, and hemostasis both to mortality prediction in patients with STEMI and NSTEMI and to the diagnosis of CMD.

Practical value: An algorithm comprising five markers with high predictive power for mortality risk in patients with STEMI and NSTEMI, based on ROC AUC (IL-1β, IL-6-R, endocan, NT-proBNP, and MMP), has been developed, along with an algorithm for predicting CMD in patients with BCCno that includes six key markers: IL-1β, IL-6-R, Apo-2, GDF-15, MMP, and von Willebrand factor/ADAMTS13. Reducing the activity of the pathogenetic mechanisms involved supports further investigation of individualized treatment.

Implementation of scientific results: Public Medical Institution Institute of Cardiology and Novamed Multidisciplinary Hospital and further scientific research at the USMF "Nicolae Testemițanu".