International Journal of
Translational Medicine

MDPI

Article

Role of NT-proBNP and Myeloperoxidase as Predictors of Abnormal Stress Test Results and Revascularization in Intermediate-Risk NSTE-ACS: A Prospective Study

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Abstract: Background: Biomarkers have emerged as a cost-effective tool to risk stratify patients presenting to the emergency department with chest pain. The measurement of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and myeloperoxidase (MPO) may improve the identification of patients who are more likely to have abnormal stress test results and require revascularization. Methods: In this prospective observational study, we evaluated the use of NT-proBNP and MPO in predicting abnormal stress testing results and revascularization in patients presenting to the ED with chest pain and an intermediate TIMI risk score. The serum levels of NT-proBNP and MPO were obtained at enrollment. Stress testing or coronary angiography was performed at the discretion of the treating physician. Clinical outcomes were followed at index hospitalization, 6 months, and 1 year. Results: A total of 485 patients were enrolled. NT-proBNP had a fair ability to predict abnormal stress testing results (AUC 0.69, $p < 0.001$). Based on the Mann–Whitney U test, there was a detectable difference in the median serum levels of both biomarkers among patients who did not undergo revascularization compared to patients who did undergo revascularization (NT-proBNP 70.5 vs. 250, $p < 0.001$, MPO 341 vs. 471, $p < 0.001$). NT-proBNP and MPO revealed a meaningful ability to predict revascularization in all patients (NT-proBNP AUC = 0.725, $p < 0.001$, MPO AUC = 0.653 $p < 0.001$). Conclusion: Elevated serum NT-proBNP was a fair predictor of abnormal stress test results. Furthermore, higher serum NT-proBNP and MPO levels were associated with revascularization events up to 1-year follow-up and were found to be meaningful predictors of coronary revascularization.

Keywords: NT-proBNP; myeloperoxidase; biomarkers; non-ST elevation acute coronary syndrome

Academic Editor: Caterina Cinti

Received: 25 November 2024
Revised: 10 January 2025
Accepted: 31 January 2025
Published: 10 February 2025

Citation: Soltero-Mariscal, E.; Sengodan, P.; Siraj, A.; Yousaf, A.; Super, D.; Penn, M.S.; Gandhi, S.; Aneja, A. Role of NT-proBNP and Myeloperoxidase as Predictors of Abnormal Stress Test Results and Revascularization in Intermediate-Risk NSTE-ACS: A Prospective Study. *Int. J. Transl. Med.* **2025**, *5*, 9. https://doi.org/10.3390/ijtm5010009

1. Introduction

In the United States, complaints of chest pain result in approximately 6.5 million emergency department (ED) visits annually [1]. The diagnosis of coronary artery disease accounts for 5.4–7.8% of such visits, and only 2.8–3.2% of the patients are diagnosed with acute myocardial infarction (AMI) [2]. Despite the use of costly tests, including stress testing, computed tomographic angiography, and invasive coronary angiography for risk assessment and prognostication, the diagnosis of AMI is missed in 0.9–2.1% of these

patients [3,4]. Among the several biomarkers in clinical practice, B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and myeloperoxidase (MPO) have shown promise in demonstrating the presence of myocardial ischemia due to atherosclerotic disease. The transcription of pro-BNP is activated during myocardial ischemia [5]. The cleavage of pro-BNP yields biologically active BNP and NT-proBNP. While both peptides undergo renal clearance, NT-proBNP is not subjected to enzymatic and receptor-mediated degradation, resulting in a longer assay window when compared to BNP [6–8]. Furthermore, the levels of NT-proBNP are not modified using the neprilysin inhibitor sacubitril [9]. Prior research evidence has proposed NT-proBNP to assist the stratification of patients with low-risk acute coronary syndrome (ACS) [10]. Meanwhile, MPO released during myocardial ischemia is an independent risk predictor for adverse cardiovascular outcomes at 30 days and 6 months [11]. This leukocyte-derived enzyme plays an important role in the development of atherosclerotic heart disease through the depletion of nitric oxide, the oxidation of lipoproteins, and the thinning of the fibrous cap resulting in plaque vulnerability [12,13]. The use of biomarkers for risk stratification may be particularly helpful in ACS patients with an intermediate TIMI score (2–5), which captures a wide range of cardiovascular risk (8.3–26.2%) [14]. In this study, we evaluate the ability of these biomarkers to predict abnormal stress test results and revascularization in intermediate-risk non-ST elevation acute coronary syndrome (NSTE-ACS).

2. Methods

This study prospectively enrolled consecutive adult patients who presented to the ED with unstable angina (UA) and intermediate risk based on a TIMI score of 2–5. The protocol was approved by the Institutional Review Board at the MetroHealth Medical Center (Registration Number IRB00000685, Approved March 2010), and informed consent was obtained from all participating patients. The clinical endpoints of this study were the detection of abnormal stress tests at enrollment, the rate of revascularization by PCI or CABG, and major adverse cardiovascular events (MACEs) at enrollment, 6 months, and 1-year follow-up. Patients were excluded if they were <18 years of age, had serum creatinine ≥ 3 mg/dL, showed clinical signs of congestive heart failure at enrollment, and non-coronary causes for troponin elevation were suspected [i.e., chest trauma, myocarditis, sepsis, and pulmonary embolism], or if inflammatory conditions were present, which could result in elevation of MPO.

Data were obtained at baseline, 1 month, 6 months, and 1 year. Clinical outcomes were assessed through phone follow-up and electronic medical record review. Key clinical data consisted of all non-invasive and invasive cardiac testing and clinical events, including angina, myocardial infarction, revascularization, and death.

Peripheral venous blood samples were collected and centrifuged, and serum aliquots were stored in a -70 °C freezer for batch assays. Biomarker testing was performed at the Cleveland HeartLab (Cleveland, OH, USA). NT-proBNP levels were measured on a COBAS e602 with reagents from Roche Diagnostics (Indianapolis, IN, USA). MPO levels were measured on a Roche COBAS c501 with turbidimetric reagents from the Cleveland HeartLab.

Stress test results were classified into three categories: abnormal, indeterminate, and normal. An abnormal test was defined by the presence of myocardial ischemia. An indeterminate test was defined by the absence of myocardial ischemia plus any of the following criteria: inability to reach the target heart rate, abnormal heart rate response, abnormal blood pressure response, or abnormal functional capacity. A normal test was defined by the absence of ischemia and none of the indeterminate criteria. Patients with an elevated troponin level and a history characteristic of acute coronary syndrome were

classified as non-ST elevation myocardial infarction (NSTEMI). Those with a characteristic history and no elevation in troponin level were classified as having unstable angina (UA).

SPSS Statistics for Windows, version 13 (SPSS Inc., Chicago, IL, USA), was used for statistical analysis. Based on the kurtosis or skewness of the data, a non-parametric Mann–Whitney test U was applied to test the significance of differences between various groups. The ROC curves of biomarkers predicting stress testing were plotted, and the area under the curve (AUC) was calculated. A similar analysis was performed to analyze the ability of biomarkers to predict revascularization at enrollment, 6 months, and 1 year.

3. Results

A total of 485 subjects who met the inclusion criteria were enrolled prospectively from 2010 to 2016. The analysis of data was performed for all patients and two subgroups based on the selected diagnostic modality for risk stratification, stress testing, or invasive coronary angiography. The baseline patient characteristics are listed in Table 1. The median NT-proBNP level in the entire cohort (n = 485) was 89 pg/mL, with an interquartile range of 32 to 259 pg/mL. The median serum MPO levels for all patients was 360 pmol/L, with an interquartile range of 289 to 517 pmol/mL. Both NT-proBNP and MPO levels were significantly higher in NSTEMI compared to those with UA (median 185 vs. 60 pg/mL for NT-pro BNP and median 465 vs. 337 pmol/L for MPO, $p < 0.001$). Among patients who were recommended coronary angiography, those with NSTEMI had higher serum levels of NT-proBNP compared to patients with UA (median 288 vs. 151 pmol/L, $p = 0.014$). The baseline NT-proBNP and MPO levels are summarized in Table 2.

Table 1. Baseline patient characteristics.

	N	Percentage (%)
Total	484	
Age		
30–64 years	350	72.2
>64 years	135	27.8
Gender		
Male	234	48.2
Female	251	51.8
Ethnicity		
White	260	53.6
Black	173	35.7
Other	52	10.7
CAD	212	43.7
MI	159	32.8
CABG	54	11.1
PCI	144	29.7
Hypertension	435	89.7
Diabetes	236	48.7
Dyslipidemia	448	92.4
Heart failure	41	8.5
Stroke	38	7.8
Smoking	327	67.4
Aspirin	360	74.2
Clopidogrel	88	18.1
Warfarin	20	4.1
Statin	344	70.9
Nitrates	140	28.9
Beta blocker	246	50.7
CCB	115	23.7
ACEI/ARB	274	56.5
Diuretics	184	37.9
Insulin	114	23.5

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CABG: coronary artery bypass grafting; CCB: calcium channel blockers; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 2. Distribution of serum NT-proBNP and MPO levels.

	NT-proBNP (pg/mL)		MPO (pmol/L)	
	Median	**IQR**	**Median**	**IQR**
All patients	88.5	32–258.5	360	289–517
UA	60	25–164	337	286–441
NSTEMI	185	85–668	465	318–724

IQR: interquartile range; MPO: myeloperoxidase; NSTEMI: non-ST elevation myocardial infarction; NT-proBNP: N-Terminal pro-B-type natriuretic peptide; UA: unstable angina.

Overall, 92 (19%) and 110 (22.7%) patients underwent coronary revascularization at enrollment and 6 months, respectively. No further revascularization events occurred at 1 year of follow-up. Patients who underwent stress testing (n = 321) had a low incidence of revascularization at enrollment (2.2%), 6 months (5%), and 1 year (5%). In the subset of patients who underwent coronary angiography (n = 164), a total of 85 (51.8%), 94 (52.4%), and 94 (52.4%) of patients were revascularized at presentation, 6 months, and 1 year, respectively. In the same subset of patients, those with NSTEMI were more likely to require revascularization compared to patients with UA (76% vs. 41%, $p < 0.001$). The breakdown of revascularization events among subjects who underwent stress testing at enrollment and those who underwent coronary angiography is listed in Table 3. The comparison of different groups using the Mann–Whitney test is summarized in Table 4.

Table 3. Revascularization by PCI or CABG at enrollment, 6 months, and 1 year.

	Number of Patients	Number of Revascularization Events		
		Enrollment	**6 Months**	**1 Year**
All patients	485	92	110	110
UA	409	38	52	52
NSTEMI	76	54	58	58
UA—Stress test *	321	7	16	16
UA—CAG **	88	31	36	36

CABG: coronary artery bypass grafting; CAG: coronary angiography; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina. * UA group in which risk stratification was performed via stress testing. ** UA group in which risk stratification was performed via coronary angiography.

Table 4. Comparison of NT-proBNP and MPO levels via revascularization in all patients and in NSTE-ACS.

No Revascularization vs. PCI/CABG			Mean Rank	Sum of Ranks	Mann–Whitney U	p
All patients	Median NT-proBNP (pg/mL)	70.5 vs. 250	220.72 vs. 329.59	86,081 vs. 30,322	9836	<0.001
	Median MPO (pmol/L)	341 vs. 471	225.79 vs. 298.62	87,605 vs. 26,876	87,605	<0.001
CAG *	Median NT-proBNP (pg/mL)	288 vs. 151	72.52 vs. 90.70	5656.5 vs. 7709.5	2575.5	0.014
	Median MPO (pmol/L)	498 vs. 415	74.57 vs. 86	5742 vs. 7138	2739	0.119

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAG: coronary angiography; MPO: myeloperoxidase; NSTE-ACS: non-ST elevation acute coronary syndrome; NT-proBNP: N-Terminal pro-B-type natriuretic peptide; PCI: percutaneous coronary intervention. * Comparison in subjects that underwent coronary angiography for risk stratification.

There were 210 (65.4%), 75 (23.4%), and 36 (11.2%) patients with normal, indeterminate, and abnormal stress tests, respectively. The median NT-proBNP levels were significantly

higher in patients with abnormal test results compared to those with normal and indeterminate results (249 vs. 89 pg/mL, $p < 0.001$). The area under the curve (AUC) of NT-proBNP was 0.69 ($p < 0.001$) for predicting abnormal stress test results. In patients with a history of CAD, the NT-proBNP ROC AUC used to predict an abnormal stress test was 0.71 (p 0.01). MPO had no predictive significance in predicting abnormal stress test results (AUC 0.49, p 0.934, Figure 1). None of the patients who underwent stress testing and had a serum NT-proBNP level less than 18 pg/mL (n = 53, 16.8%) required revascularization at enrollment, 6 months, or 1 year. Furthermore, no patient with a history of CAD and with a serum NT-proBNP of less than 46 pg/mL (n = 32, 26.4%) had an abnormal stress test.

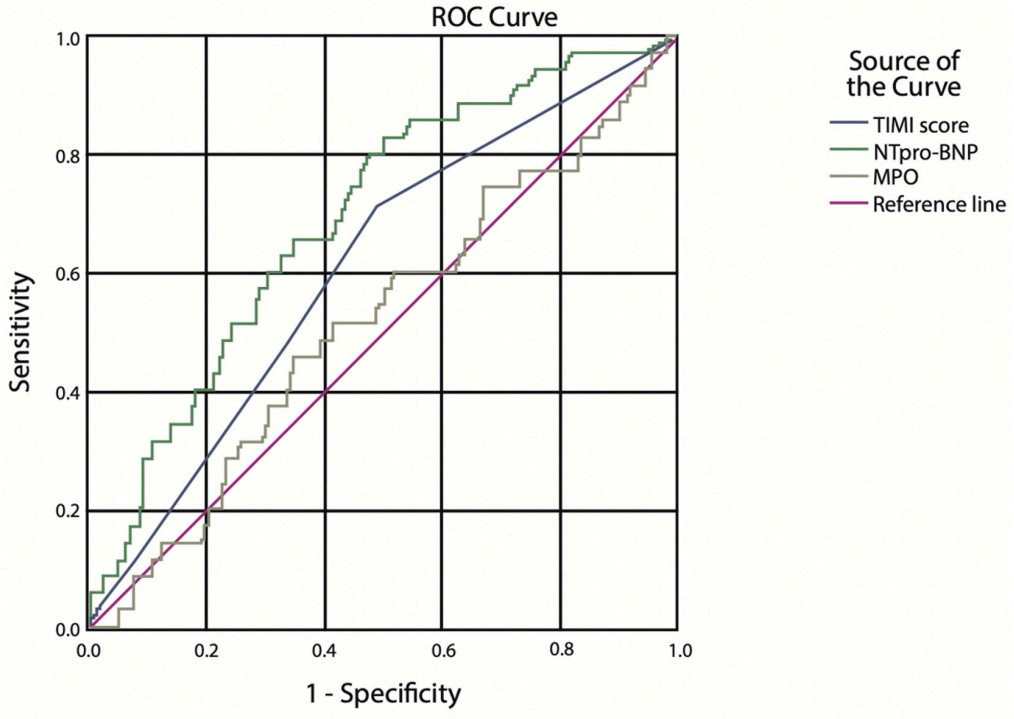

Figure 1. ROC curves of biomarkers predicting abnormal stress tests.

The median serum NT-proBNP level was significantly higher in patients who underwent revascularization at enrollment compared to those not requiring revascularization (250 vs. 70.5 pmol/L, $p < 0.001$). Similarly, the median MPO level was significantly higher in patients who underwent revascularization compared to those who did not require revascularization (471 vs. 341 pmol/L, $p < 0.001$). The AUC for NT-proBNP to predict revascularization in all patients was 0.72, 0.73, and 0.73 ($p < 0.001$) at enrollment, six months, and one year, respectively (Figure 2). The AUC for baseline MPO levels to predict revascularization in all patients was 0.65, 0.64, and 0.64 at enrollment, six months, and one year, respectively ($p < 0.001$).

In the subgroup of patients who were recommended coronary angiography, NT-proBNP levels were significantly higher in patients who required revascularization (median 288 vs. 151 pg/mL $p = 0.012$). The AUC predicting revascularization was 0.62 ($p = 0.012$) at presentation and remained at 0.62 ($p = 0.011$) at 6 months. In this same group, the difference in the median baseline MPO levels was not statistically significant in patients who underwent revascularization compared to those who did not undergo revascularization (498 vs. 415 pmol/L, $p = 0.119$). The results of the AUC predicting revascularization for MPO and NT-proBNP at enrollment and at six months are summarized in Table 5. The description of the findings in coronary angiography is summarized in Table 6.

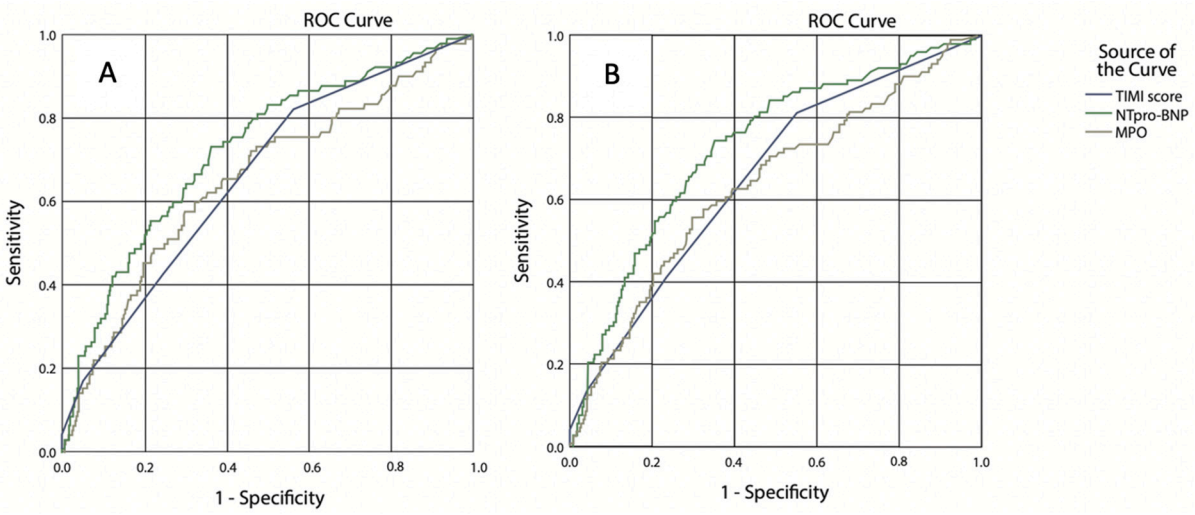

Figure 2. ROC of biomarkers predicting revascularization in all patients at enrollment (**A**) and at 6 months (**B**).

Table 5. Area under the curve for revascularization in all patients.

Test Result Variable(s)	Area	Std. Error	*p*-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Enrollment					
TIMI score	0.661	0.031	<0.001	0.599	0.72
NT-proBNP	0.725	0.03	<0.001	0.666	0.784
MPO	0.653	0.034	<0.001	0.588	0.719
6 months					
TIMI score	0.658	0.03	<0.001	0.599	0.716
NT-proBNP	0.731	0.028	<0.001	0.676	0.786
MPO	0.636	0.032	<0.001	0.573	0.699
Null hypothesis: true area = 0.5					

MPO: myeloperoxidase; NT-proBNP: N-Terminal pro-B-type natriuretic peptide; TIMI: thrombolysis in myocardial infarction.

Table 6. Coronary angiography results.

Total	155 (32%)
Non-obstructive disease	54
Single vessel	27
Two vessel	18
Three vessel	56
LMCA	4
LAD	58
Lcx	43
RCA	45

NT-proBNP failed to predict MACE at 1 year. A total of 23 patients had MACEs at 1 year (death = 7; stroke = 3; MI = 4; revascularization = 18). There was no significant difference in either NT-proBNP ($p = 0.19$) or MPO ($p = 0.60$) compared to those without MACEs either as a composite event group or four subgroups.

4. Discussion

Our results indicate that NT-ProBNP is an independent predictor of abnormal stress test results in patients with chest pain and an intermediate TIMI risk score presenting to the ED. Importantly, the predictive ability of NT-ProBNP was only mildly improved in the

group of patients with a history of coronary artery disease, which supports the strength of its independent association with ischemia. The mean serum NT-proBNP levels were significantly higher in patients with abnormal stress test results compared to those with indeterminate or normal results. Furthermore, an NT-proBNP level of less than 46 pg/mL accurately ruled out the likelihood of abnormal results. These findings supplement the available evidence of NT-proBNP as an independent marker of obstructive coronary artery disease and inducible ischemia [15].

Once validated, the use of this readily available test could help the clinician streamline the decision to obtain stress testing in patients presenting to the ED with chest pain. The implementation of NT-proBNP in the evaluation of intermediate-risk chest pain could offer more judicious use of functional testing, leading to a downstream reduction in false positive results. It could also identify patients at higher risk of having obstructive coronary artery disease, who are more likely to benefit from a demonstration of coronary anatomy (i.e., coronary computed tomography angiography, invasive coronary angiography). Moreover, we see an opportunity to reduce the healthcare costs associated with the evaluation of chest pain in the emergency department.

The median serum levels of NT-proBNP and MPO were significantly higher in NSTEMI compared to UA, suggesting that these biomarkers increase in correlation with the extension of myocardial ischemia. The mechanism for the increase in NT-proBNP may be explained by the enhanced transcription of BNP mRNA in the peri-infarct zone demonstrated in animal studies of AMI [5]. A prior study comparing BNP levels after exercise stress testing and myocardial perfusion imaging in patients with and without obstructive CAD showed higher levels of this biomarker in those with obstructive disease. Furthermore, the magnitude of the increase in serum BNP correlated with the severity of ischemia [16]. The primary triggers for this enhanced transcription are myocardial stretching and neurohormonal activation, both of which are well-established consequences of myocardial ischemia [17]. Elevated left ventricular end-diastolic pressure, diastolic dysfunction, myocardial thinning, and the resulting increased wall stress of inadequately perfused ventricular muscle contribute to increased BNP levels [18]. Additionally, hypoxia has been shown to stimulate the release of BNP in patients with cyanotic congenital heart disease and normal filling pressures [19]. The higher serum MPO levels in the group of patients with NSTEMI are likely the result of a higher prevalence of plaque disruption in this group. In a previous study of patients who suffered sudden coronary death, increased numbers of MPO-containing cells and neutrophils were found in plaque rupture sites compared to a thin cap and thick fibrous cap atheroma [20].

Both biomarkers demonstrated a detectable ability to predict revascularization in all patients at enrollment and during follow-up (Table 5). The AUC for NT-proBNP had a better performance than the TIMI score and MPO, showing a considerable ability to predict revascularization in all patient analyses (Table 5). The low rate of PCI/CABG at enrollment in the group of patients who underwent stress testing precluded an accurate analysis of the ability of NT-proBNP to predict index revascularization. However, after six months of follow-up, there was an increase in the number of PCI/CABG, which helped us conclude that higher NT-proBNP levels were associated with revascularization events. The subset of patients that were recommended coronary angiography as the initial risk stratification strategy had the highest revascularization rate in our cohort. This group likely captured patients with more extensive ischemic burden. Within this group, NT-proBNP showed a fair ability to predict revascularization as the AUC outperformed the TIMI score.

MPO identifies vulnerable plaque and predictably fails to identify patients with abnormal stress test results. Consistent with its role in identifying ACS [21], MPO did show significant value in predicting revascularization in an all-patient analysis. These

results supplement the existent evidence of higher MPO levels both in unstable compared to stable angina [22,23] and in NSTE-ACS compared to STEMI [24]. In addition, serum MPO levels have been associated with the extension of coronary artery disease and plaque disruption in patients with unstable angina [25]. In contrast to this previous evidence, MPO failed to provide a meaningful diagnostic utility in ACS patients in a previous multicenter prospective study [26]. Our results are limited to intermediate TIMI risk scores and suggest that progressively higher values of this biomarker correlate with the ischemic burden in NSTE-ACS.

During 1-year follow-up, we did not find a detectable difference in serum biomarker levels and MACEs. Nevertheless, this study was not designed to evaluate the association of serum biomarkers with adverse cardiovascular outcomes. In addition, the low number of adverse events limits the power to detect such differences within our patient cohort. We defer to the current literature, which supports the association of NT-proBNP and MPO with worse cardiovascular outcomes across the spectrum of ACS [27–30].

In our study of the use of NT-proBNP and MPO to predict abnormal stress test results and revascularization in patients with chest pain and intermediate TIMI scores, a low–normal NT-proBNP is a particularly useful biomarker to predict normal stress test results. NT-proBNP is a good predictor of revascularization in patients with NSTE-ACS and intermediate TIMI scores. In contrast, MPO had a modest ability to predict revascularization in all patients. Our study supports the use of NT-proBNP and MPO to risk stratify patients presenting with chest pain to the ED. Further prospective studies are needed to validate these results.

There are limitations to be acknowledged in our observational study. First, only intermediate-risk patients were enrolled; therefore, our results cannot be applied to patients presenting a low (0–1) or high TIMI score (6–7). However, the management of low-risk and high-risk patients is less controversial. Our study was conducted at a single institution, which necessitates confirmation in larger studies. Although none of the patients with a low NT-proBNP had an abnormal stress test, we are unable to firmly recommend a discrete cutoff value that would preclude the need for stress testing. We were also unable to assess the association between serum biomarker levels with MACEs given the modest sample size and low number of adverse events. Importantly, our study was performed before the implementation of a high-sensitivity cardiac troponin (hs-cTn) assay at our institution. Using hs-cTN would have increased the number of patients diagnosed with NSTEMI, modifying the utilization of functional testing and coronary angiography. In a previous observational study, the diagnosis of type 1 myocardial infarction increased 1.7-fold with the use of hs-cTN compared to a fourth-generation troponin assay [31]. Despite the increased sensitivity for the detection of myocardial injury, routine hs-cTn use had a non-significant clinical impact in a recent randomized trial of low-risk patients with chest pain [32,33]. Biomarkers have emerged as a cost-effective tool for cardiovascular risk stratification, optimizing resource utilization and patient outcomes [34]. Finally, the results of our study do not apply to patients with severely impaired renal function and those with reduced cardiac function.

Author Contributions: Methodology, A.A.; software, E.S.-M.; formal analysis, investigation, P.S. and E.S.-M.; resources, M.S.P.; data curation, P.S., A.S., A.Y. and D.S.; writing—original draft preparation, E.S.-M. and A.A.; writing—review and editing, E.S.-M., P.S. and A.A.; visualization, D.S.; supervision, A.A.; project administration, S.G.; funding acquisition, M.S.P. and S.G. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported in part by funds from the Cleveland HeartLab, Inc. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of MetroHealth Medical Center Institutional Review Board—Registration Number IRB00000685.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data is available securely in folders and in the form of encrypted software in the form of databases.

Conflicts of Interest: Dr. Marc S. Penn was the founder and chief medical officer of Cleveland HeartLab, Inc. The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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