Laboratory markers at admission to predict the presence of totally occluded culprit artery in NSTEMI

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Abstract
A significant proportion of patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI) have a totally occluded culprit artery (OCA). If these patients do not meet very high-risk criteria, they may be deprived of an immediate invasive strategy. Therefore, there is a need for markers that can predict OCA in patients with NSTEMI. A total of 357 consecutive patients with NSTEMI but without very high-risk criteria were included in this retrospective study. Two groups were formed: NSTEMI with OCA (n = 106) and NSTEMI with patent culprit artery (PCA) (n = 251). Complete blood count (CBC) and serum biochemical parameters obtained immediately at admission were compared between the groups. Receiver operating characteristic (ROC) analysis to predict the presence of OCA was performed for the parameters that were significantly different between the groups, and an area under the curve (AUC) > 0.7 was considered to suggest acceptable discrimination. Neutrophil count [8.13 (2.82-27.88) × 10^3/µL vs 5.59 (1.85-19.71) × 10^3/µL, P < .001] and aspartate aminotransferase (AST) level [45 (12-405) U/L vs 25 (5-143) U/L, P < .001] were significantly higher in patients with OCA. The AUC was 0.750 for neutrophil count and 0.731 for AST level. The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of elevated neutrophil and/or AST levels for the presence of OCA were 77.4%, 70.1%, 52.2%, and 88.0%, respectively. More strikingly, the specificity was 95.2% in the presence of both neutrophil and AST elevation. Elevated neutrophil and/or AST levels at admission were strongly associated with the presence of OCA in patients with NSTEMI.

Abbreviations: ACS = acute coronary syndrome, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the curve, CBC = complete blood count, ICA = invasive coronary angiography, MI = myocardial infarction, NLR = neutrophil-to-lymphocyte ratio, NPV = negative predictive value, NSTEMI = non-ST-segment elevation myocardial infarction, OCA = occluded culprit artery, PCA = patent culprit artery, PCI = percutaneous coronary intervention, PLR = platelet-to-lymphocyte ratio, ROC = receiver operating characteristic, RVD = reference vessel diameter, STEMI = ST-segment elevation myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction, URL = upper reference limit, WBC = white blood cell.

Keywords: aspartate aminotransferase, neutrophil count, NSTEMI, occluded culprit artery

1. Introduction
Acute coronary syndrome (ACS) can manifest in three ways: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. Totally occluded culprit arteries (OCA) in the setting of ACS usually present with STEMI, and current guidelines recommend an immediate invasive strategy for patients with STEMI.[1] However, about 30% of patients with NSTEMI have an OCA as well,[2,3] but these patients may be deprived of an immediate invasive strategy if they do not meet very high-risk criteria.[4] Considering the worse prognosis in NSTEMI with OCA compared to NSTEMI with patent culprit artery (PCA),[2,3] delayed revascularization may be deleterious for these patients. Therefore, it is important to predict patients with OCA at the time of admission. Several electrocardiographic findings that may be indicative of the presence of OCA in NSTEMI have been suggested.[1] Nevertheless, better tools that can predict these patients are required to enable earlier revascularization and potentially improve prognosis. Therefore, in the present study, we aimed to compare NSTEMI patients with OCA and NSTEMI patients with PCA in terms of complete blood count (CBC) and serum biochemical parameters obtained immediately at admission to identify a possible marker that can predict the presence of OCA in this setting.

2. Methods
After obtaining approval from the institutional ethics committee, patients who underwent invasive coronary angiography
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Prior PCI (%*) 20 (18.9) 64 (25.5) .177

GFR = glomerular filtration rate; HbA1c, glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; OCA = occluded culprit artery; PCA = patent culprit artery; PCI = percutaneous coronary intervention.

### 3. Results

#### 3.1. Baseline characteristics of the study groups were similar (Table 1).

Total white blood cell (WBC) count, neutrophil count, neutrophil percentage, neutrophil-to-lymphocyte ratio (NLR), monocyte count, and platelet-to-lymphocyte ratio (PLR) were significantly higher ($P < .001$, $P < .001$, $P < .001$, and $P = .037$, respectively); lymphocyte percentage, monocyte percentage, eosinophil count, eosinophil percentage, and basophil percentage were significantly lower ($P < .001$, $P = .009$, $P < .001$, $P < .001$, and $P < .001$, respectively) in patients with OCA. The OCA group had higher glucose, AST, alanine aminotransferase (ALT), and AST/ALT ratio ($P = .005$, $P < .001$, $P < .001$, and $P < .001$, respectively), but lower sodium ($P < .001$) (Table 2).

Time from admission to ICA was comparable between the groups. LAD as the culprit artery was more common in patients with PCA ($P < .001$), and RCA as the culprit artery was more common in patients with OCA ($P = .002$). RVD was larger in the PCA group ($P = .001$) (Table 3).

#### Table 1

| Variable                        | NSTEMI with OCA (n = 106) | NSTEMI with PCA (n = 251) | $P$   |
|---------------------------------|---------------------------|---------------------------|-------|
| Age (year)                      | 61.5 ± 13.1               | 61.5 ± 10.9               | .964  |
| Gender                          |                           |                           |       |
| Male (%)                        | 81 (76.4)                 | 185 (73.7)                | .591  |
| Female (%)                      | 25 (23.6)                 | 66 (26.3)                 |       |
| Hypertension (%)                | 47 (44.3)                 | 125 (49.8)                | .345  |
| Diabetes (%)                    | 37 (34.9)                 | 81 (32.3)                 | .629  |
| HbA1c (%)                       | 5.9 (4.8-12.0)            | 6.0 (4.6-16.9)            | .941  |
| Total cholesterol (mg/dL)       | 182.1 ± 43.8              | 177.9 ± 40.5              | .413  |
| LDL cholesterol (mg/dL)         | 108.8 ± 37.2              | 106.1 ± 33.2              | .353  |
| HDL cholesterol (mg/dL)         | 37 (17-68)                | 36 (21-78)                | .192  |
| Triglyceride (mg/dL)            | 158 (44-869)              | 149 (38-1010)             | .413  |
| Chronic kidney disease (%)      | 11 (10.6)                 | 29 (11.6)                 | .747  |
| GFR (mL/min/1.73 m²)            | 82.6 ± 22.6               | 84.5 ± 26.2               | .516  |
| Prior PCI (%)                   | 20 (18.9)                 | 64 (25.5)                 | .177  |

*Column percentage.

GFR = glomerular filtration rate; HbA1c, glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; OCA = occluded culprit artery; PCA = patent culprit artery; PCI = percutaneous coronary intervention.
ROC analysis revealed that the AUC values of neutrophil count, total WBC count, and AST level were >0.7 (0.750, 0.736, and 0.731, respectively) (Table 4).

The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of elevated neutrophil and/or AST levels for the presence of OCA were 77.4%, 70.1%, 52.2%, and 88.0%, respectively. When looking at other remarkable values, elevated neutrophil had an NPV of 81.6%, elevated AST had a specificity of 85.7%, and elevated neutrophil and AST had a specificity of 95.2% (Table 5).
4. Discussion

The present study has revealed that elevated neutrophil and/or AST levels at admission can predict the presence of OCA with a sensitivity of 77.4% and a specificity of 70.1% in NSTEMI patients without very high-risk criteria. More strikingly, the specificity was 95.2% in the presence of both neutrophil and AST elevation.

CBC parameters have been investigated in many clinical studies on acute MI. In a study that included patients presenting with STEMI, total WBC count at admission was found to be an independent predictor of infarct size and baseline TIMI grade 0/1 flow in the culprit artery, but no data on differential WBC count were available.[7] In another study that included patients with acute MI undergoing primary PCI, total WBC count, neutrophil count, neutrophil percentage, and NLR were significantly higher and lymphocyte percentage was significantly lower in patients with OCA than in patients with PCA, in line with our study. In addition, elevated neutrophil count at admission was found to be an independent predictor of total coronary occlusion in patients with acute MI undergoing primary PCI in the aforementioned study.[8] NLR[9–12] and PLR[10] have also been suggested in clinical studies as predictors of culprit artery patency in STEMI. The vast majority of the patient population in all these studies consisted of STEMI patients who already had an indication for an immediate invasive strategy. In contrast, our study population consisted of NSTEMI patients without very high-risk criteria, so there was no indication for an immediate invasive strategy according to current guidelines.[4] In our study, many significant differences were detected between the groups in terms of CBC parameters at admission. Total WBC count, neutrophil count, neutrophil percentage, NLR, monocyte count, and PLR were significantly higher; lymphocyte percentage, monocyte percentage, eosinophil count, eosinophil percentage, and basophil percentage were significantly lower in the OCA group. However, only neutrophil count and total WBC count were considered to suggest acceptable discrimination (AUC > 0.7) between patients with OCA and those with PCA, according to our study design. Since they increase in line with each other due to a possible inflammatory response and the AUC value of neutrophil count (0.750) was higher than that of total WBC count (0.736), neutrophil count has been more emphasized as a predictor of OCA in the present paper. In the literature, red cell distribution width has also been suggested as a predictor of OCA in acute MI,[13,14] but it was comparable between the groups in our study.

We have demonstrated that elevated AST level at admission can also predict the presence of OCA in NSTEMI patients without very high-risk criteria. Historically, AST was the first cardiac biomarker to be used for acute MI diagnosis,[15] but it has been substituted by more sensitive tests over time. Because the myocardium has high AST activity, myocardial necrosis may cause an increase in serum AST level. However, serum AST level does not increase in every patient with acute MI. In a study investigating the pattern of liver enzyme elevations in STEMI, 86% of patients had elevated AST within 24 hours of admission.[16] In another study investigating the effect of AST on prognosis in NSTEMI, only 33% of patients had elevated AST within 24 hours of admission. In addition, AST was found to be a stronger predictor of in-hospital mortality than troponin peak in the aforementioned study, but no data on culprit artery patency were available.[17] It is obvious that further studies are needed to better understand what AST elevation means, particularly in NSTEMI. In our study, ALT and AST/ALT ratio were also

| Table 4 |
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| ROC analysis for predicting totally occluded culprit artery in NSTEMI. |
| Variable | AUC | 95% CI | P |
| Neutrophil count | 0.750 | 0.690-0.805 | <.001 |
| Total WBC count | 0.736 | 0.678-0.795 | <.001 |
| AST | 0.731 | 0.669-0.792 | <.001 |
| Neutrophil percentage | 0.686 | 0.628-0.744 | <.001 |
| NLR | 0.686 | 0.627-0.745 | <.001 |
| Lymphocyte percentage | 0.682 | 0.623-0.742 | <.001 |
| AST/ALT ratio | 0.676 | 0.609-0.743 | <.001 |
| Eosinophil percentage | 0.860 | 0.597-0.722 | <.001 |
| Basophil percentage | 0.644 | 0.581-0.707 | <.001 |
| Eosinophil count | 0.618 | 0.547-0.678 | <.001 |
| ALT | 0.612 | 0.548-0.674 | <.001 |
| Sodium | 0.611 | 0.531-0.656 | <.005 |
| Glucose | 0.593 | 0.519-0.659 | <.008 |
| Monocyte count | 0.589 | 0.524-0.652 | <.009 |
| Monocyte percentage | 0.588 | 0.504-0.636 | .037 |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the curve, CI = confidence interval, NLR = neutrophil-to-lymphocyte ratio, NSTEMI = non-ST-segment elevation myocardial infarction, PLR = platelet-to-lymphocyte ratio, ROC = receiver operating characteristic, WBC = white blood cell.

| Table 5 |
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| Sensitivity, specificity, and predictive values of elevated neutrophil and AST levels at admission for predicting totally occluded culprit artery in NSTEMI. |
| Variable | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
| Elevated neutrophil | 57.5 | 79.6 | 54.5 | 81.6 |
| Elevated AST | 47.2 | 85.7 | 58.1 | 79.3 |
| Elevated neutrophil and AST | 27.4 | 95.2 | 70.7 | 75.6 |
| Elevated neutrophil and/or AST | 77.4 | 70.1 | 52.2 | 88.0 |

AST = aspartate aminotransferase, NPV = negative predictive value, NSTEMI = non-ST-segment elevation myocardial infarction, PPV = positive predictive value.
higher in patients with OCA. The OCA group had higher serum glucose, likely due to higher stress, and lower serum sodium, likely due to higher serum glucose. In the literature, AST/ALT ratio\cite{17} and serum glucose level\cite{18} at admission have also been suggested as predictors of culprit artery patency in acute MI. However, in our study, none of the serum biochemical parameters at admission other than AST were capable enough to distinguish between patients with OCA and those with PCA, according to our study design.

In patients with acute MI, a possible increase in neutrophil count begins within a few hours after symptom onset,\cite{19} and a possible increase in serum AST level begins 3 to 4 hours after symptom onset.\cite{20} So neutrophil count may better predict the presence of OCA in patients presenting early after symptom onset, and serum AST level may provide additional information in patients presenting later. Therefore, considering patients presenting at different time periods after symptom onset, we also combined elevated neutrophil and AST levels when determining the sensitivity, specificity, and predictive values. Additionally, in the present study, we did not determine new cutoff values for neutrophil count and serum AST level and acted according to the reference cutoff values determined for the kits used. The URL of neutrophil count and serum AST level and acted according to the reference cutoff values determined for the kits used. The URL of neutrophil count and serum AST level was 46 U/L for both men and women.

Our findings imply that elevation in neutrophil count and serum AST level may be suggestive of OCA and transmural myocardial injury in NSTEMI. Therefore, an immediate invasive strategy may be considered in these patients. Additional measurements 3 to 6 hours after symptom onset may increase the sensitivity and enable earlier revascularization. To our knowledge, this is the first study to associate AST elevation with the presence of OCA in NSTEMI.

Our study had some limitations. This was a retrospective single-center study with relatively small sample size. We did not have data regarding the time from symptom onset to admission. Cardiac troponin levels at admission were not evaluated in this study because various kits had been used at our center in the specified period. Finally, the study population consisted of highly selected patients; therefore, our findings may not be applicable to all patients with NSTEMI.

In conclusion, elevated neutrophil and/or AST levels at admission were strongly associated with the presence of OCA in patients with NSTEMI. However, prospective studies are required to better understand the course of neutrophil count and serum AST level in NSTEMI with OCA and NSTEMI with PCA.

**Author contributions**

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