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ANALIZA PRZYDATNOŚCI DIAGNOSTYCZNEJ I PREDYKCYJNEJ WYBRANYCH BIOMARKERÓW W ODNIESIENIU DO PACJENTÓW Z OSTRYMI ZESPOŁAMI WIEŃCOWYMI

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ANALYSIS OF THE DIAGNOSTIC AND PREDICTIVE UTILITY OF SELECTED BIOMARKERS FOR PATIENTS WITH ACUTE CORONARY SYNDROMES

Introduction

Acute coronary syndromes (ACS) remain one of the leading causes of morbidity and mortality worldwide, posing significant diagnostic and therapeutic challenges. Effective diagnosis and accurate risk stratification of patients with suspected ACS are crucial for optimizing treatment strategies and improving prognosis. Currently, one of the basic diagnostic components, besides clinical symptoms and electrocardiography (ECG) of ACS, remains cardiac biomarkers, particularly cardiac troponins (cTn), which are the gold standard for identifying myocardial damage. However, due to the heterogeneity of patient populations and the complexity of the pathophysiological mechanisms underlying ACS, it is necessary to search for additional biomarkers with diagnostic and prognostic potential.

In recent years, numerous studies have pointed out the important role of inflammatory parameters, hematological parameters, and metabolic indicators in the evaluation of patients with ACS. Biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-based ratios, monocyte-to-HDL cholesterol ratio (MHR), cystatin C (CysC), galectin-3, soluble urokinase-type plasminogen activator receptor (suPAR), and endocan (ESM-1) can provide valuable information on inflammatory processes, endothelial dysfunction, coagulation mechanisms, and atherosclerotic plaque destabilization. Integration of these parameters with classical cardiac markers can increase diagnostic sensitivity and specificity, as well as improve the prediction of cardiovascular complications such as reinfarction, heart failure, and mortality.

Objective

To evaluate the diagnostic and prognostic value of selected biomarkers in acute coronary syndromes (ACS) and their potential use in patient risk stratification, optimization of treatment strategies, and prediction of cardiovascular complications.

Material and methods

This series of monothematic publications includes one retrospective study and seven systematic reviews of the literature with meta-analyses, focusing on the diagnostic and prognostic role of various biomarkers in acute coronary syndromes (ACS).

The aim of the first study was to evaluate the diagnostic and prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in patients with acute coronary syndromes. For this purpose, a systematic review of the literature with meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Databases were searched: PubMed Central, Medline, Scopus, EMBASE, and Cochrane Central. The research protocol was approved in advance by all authors and registered in the international PROSPERO database (CRD42023468529). Only articles published in English in peer-reviewed journals were included in the analysis, while publications in other languages and papers in the nature of editorials, letters to the editor, case reports, pediatric population studies, narrative reviews, and conference proceedings were excluded. A search of databases identified 1148 potential references. After the selection process, 90 articles covering a total of 45,990 patients were included in the final analysis.

Another analysis focused on evaluating the prognostic value of the platelet-to-lymphocyte ratio (PLR) in patients with acute coronary syndromes. Similar to the first study, we conducted a systematic literature review with meta-analysis and prospectively registered its protocol in the PROSPERO database (CRD42023447572). The search strategy included the same databases—PubMed Central, Medline, Scopus, EMBASE, and Cochrane Central—with the additional inclusion of Google Scholar. Only articles published in English that compared PLR values in patients with ACS

were included in the analysis, with the exclusion criteria remaining the same as in the previous study. A search of the databases identified 2236 articles. After the elimination of duplicates and selection based on titles and abstracts, followed by a full evaluation of the selected publications, 19 articles were included in the final analysis.

The third study was retrospective and was conducted to evaluate the usefulness of platelet-derived indices in differentiating patients with acute coronary syndrome, classified into STEMI and NSTEMI groups. The analysis included patients hospitalized in the Department of Cardiology and Internal Medicine at the University Hospital No. 1 in Bydgoszcz between September 1 and December 21, 2023. Clinical and laboratory data were retrospectively obtained from electronic medical records. Sixty-five patients were included in the study, of whom 25 met criteria for STEMI and 40 were classified as NSTEMI. To determine the diagnostic ability of selected indicators in differentiating STEMI and NSTEMI, Receiver Operating Characteristic (ROC) curve analysis was performed. The value of the area under the curve (AUC) was calculated for each indicator, and optimal cutoff values were determined based on Youden's index to estimate their sensitivity and specificity.

The fourth analysis focused on assessing the prognostic value of the monocyte-to-high-density lipoprotein ratio (MHR) in patients with acute coronary syndromes. For this purpose, a systematic review of the literature with meta-analysis was conducted according to PRISMA guidelines, and the study protocol was prospectively registered in the PROSPERO database (CRD42023480204). Publications indexed in PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library databases were analyzed to identify studies on the association of MHR with the prognosis of patients with ACS. The search strategy was designed to include a wide range of synonyms and key terms related to both MHR and ACS to obtain the most comprehensive dataset possible. We included 11 studies involving a total of 7421 patients in the full analysis, eliminating duplicates and pre-selecting based on titles and abstracts.

The fifth analysis focused on evaluating the diagnostic and prognostic value of cystatin C (CysC) in patients with acute coronary syndromes. For this purpose, a systematic literature review with meta-analysis was conducted according to PRISMA guidelines, and the study protocol was prospectively registered in the PROSPERO database (CRD42024575092). To assess the utility of cystatin C as a diagnostic and prognostic marker in the ACS patient population, a comprehensive literature search was conducted in PubMed, Web of Science, Cochrane Library, and Embase databases. The search strategy was carefully designed to include a wide range of synonyms and key terms related to both cystatin C and various forms of ACS, including STEMI, NSTEMI, and UAP. The search was limited to articles published by August 1, 2024, and included only English-language publications. After the elimination of duplicates and pre-selection based on titles and abstracts, 59 studies, involving a total of 43,189 patients, were eligible for full analysis. Inclusion criteria included cohort and case-control studies that analyzed cystatin C levels in relation to clinical outcomes of patients with ACS.

The sixth analysis, also conducted as a systematic literature review with meta-analysis, focused on a detailed evaluation of the diagnostic and prognostic value of cystatin C (CysC) in patients with acute coronary syndromes (ACS). Cystatin C, as a biomarker involved in inflammation, oxidative stress, and endothelial dysfunction, is of increasing interest as a potential prognostic indicator in cardiology. As in previous analyses, the study was conducted according to PRISMA guidelines, and the protocol was prospectively registered in the PROSPERO database (CRD42024575092). The literature review included PubMed, Web of Science, Cochrane Library, and Embase databases, and the search strategy was optimized to include a broad spectrum of synonyms and terms related to CysC and ACS (STEMI, NSTEMI, UAP). The full analysis included 59 studies, involving a total of 43,189 patients, after removing duplicates and pre-selection based on titles and abstracts. Inclusion criteria included cohort and case-control studies that analyzed cystatin C levels

in the context of clinical outcomes of patients with ACS. Only studies providing detailed data on CysC levels and its association with patient prognosis, including cardiovascular complications such as mortality, reinfarction, heart failure, and the need for repeat revascularization, were included.

The seventh analysis focused on evaluating the diagnostic value of soluble urokinase-type plasminogen activator receptor (suPAR) as a biomarker of acute coronary syndromes. Modern medicine is striving to identify new biomarkers with high prognostic and diagnostic value that could improve the early diagnosis of ACS and risk stratification in patients hospitalized with suspected myocardial infarction. SuPAR, as a marker of immune system activation and inflammation, is of growing interest for its potential role in cardiovascular disease. As in previous meta-analyses, the study was conducted according to PRISMA guidelines, and its protocol was prospectively registered in the PROSPERO database (CRD42023431413). In order to comprehensively evaluate the utility of suPAR as a diagnostic marker in ACS, a systematic literature search was conducted in the Web of Science, PubMed, Scopus, and Cochrane Central Register of Controlled Trials databases. In addition, to increase the completeness of the review, results from Google Scholar were analyzed, and reference lists of selected publications were manually searched. The search strategy included a wide range of synonyms and key terms related to both suPAR and various forms of ACS, including STEMI, NSTEMI, and unstable angina (UA). After the elimination of duplicates and selection based on titles and abstracts, five studies involving a total of 3,417 patients were eligible for full analysis. Inclusion criteria included cohort and case-control studies that compared suPAR levels in patients with ACS and controls. Only publications providing detailed data on suPAR concentrations and its relationship to patients' clinical outcomes were included, as well as studies reporting the relationship of suPAR with cardiovascular complications such as mortality, reinfarction, and heart failure.

The eighth and final publication evaluated the diagnostic and prognostic value of endocan (ESM-1) in patients with ACS. As a marker of endothelial dysfunction and inflammatory processes, endocan is of growing interest in the context of myocardial infarction progression and patient risk assessment. As in previous meta-analyses, the study was conducted according to PRISMA guidelines, and the protocol was registered in the PROSPERO database (CRD42024575085). The systematic review included publications indexed in PubMed, Scopus, Embase, and the Cochrane Library, focusing on endocan in different forms of ACS (STEMI, NSTEMI, unstable angina). After selecting the literature, we selected four studies involving 741 patients for final analysis. The results indicate that endocan may play an important role in the mechanisms of plaque destabilization and prognosis in ACS, which requires further clinical studies.

Results

The first study to evaluate the diagnostic and prognostic value of the NLR index in the context of ACS showed significant differences in its levels. NLR levels were significantly higher in patients with ST-segment elevation myocardial infarction (STEMI) compared to non-ST-segment elevation myocardial infarction (NSTEMI) patients (4.94 ± 3.24 vs. 3.24 ± 2.74). A similar trend was observed among patients with acute myocardial infarction (AMI), where NLR values exceeded those recorded in those with unstable angina (4.47 ± 3.43 vs. 2.97 ± 1.58). Also, among patients with ACS, the NLR index was significantly higher compared to patients with stable angina (SAP) (5.45 ± 4.28 vs. 2.46 ± 2.15) and control subjects (5.31 ± 4.01 vs. 2.46 ± 2.45). In addition, there was a significant correlation between NLR levels and mortality in ACS—patients who survived had significantly lower index values compared to those who died (3.67 ± 2.72 vs. 5.56 ± 3.93). Subgroup analysis also showed that among STEMI patients, survivors had lower NLR rates than those who died (4.28 ± 3.24 vs. 6.79 ± 3.98). A similar relationship was observed in the context of major cardiovascular incidents (MACE). Patients with ACS who experienced MACE had a higher NLR compared to those without such events (6.29 ± 4.89 vs. 3.82 ± 4.12). In the STEMI group, patients who experienced MACE also had significantly higher NLRs compared to those without complications (6.99 ± 5.27 vs. 4.99 ± 4.12).

The second study, evaluating the potential prognostic role of the platelet-to-lymphocyte ratio (PLR) in patients with suspected ACS, showed that PLR values were significantly higher in patients who had experienced major cardiovascular events (164.0 ± 68.6) compared to those without such events (115.3 ± 36.9; MD = 40.14; 95% CI: 22.76-57.52; p < 0.001). The analysis also showed that patients with acute myocardial infarction (AMI) who died had a significantly higher PLR value (183.3 ± 30.3) than those who survived (126.2 ± 16.8; MD = 39.07; 95% CI: 13.30-64.84; p = 0.003). A similar trend was observed when comparing patients with ACS to controls, where mean PLR levels were significantly higher in the ACS group (168.2 ± 81.1 vs. 131.9 ± 37.7; MD = 39.01; 95% CI: 2.81-75.21; p = 0.03). Subgroup analysis also showed differences in PLR levels between STEMI and NSTEMI patients, but the difference did not reach statistical significance (165.5 ± 92.7 vs. 159.5 ± 87.8; MD = 5.98; 95% CI: -15.09-27.04; p = 0.58). Similarly, a comparison of PLR values between patients with myocardial infarction (MI) and those with unstable angina (UAP) indicated higher PLR values in the MI group (162.4 ± 90.0 vs. 128.2 ± 64.9), but this difference was also not statistically significant (MD = 18.28; 95% CI: -8.16-44.71; p = 0.18).

The third study showed that the leukocyte count (WBC) had the highest discriminatory power (AUC: 0.78) with a threshold value of 10.56, with a sensitivity of 84% and specificity of 80%. Strong correlations were found between LDL cholesterol (LDL-C) and total cholesterol (r = 0.96) and between hemoglobin and hematocrit (r = 0.95). Moderate correlations were observed between leukocyte count (WBC) and platelet count (PLT) (r = 0.52) and between PLT and platelet-to-leukocyte ratio (PLT-to-WBC) (r = 0.38). In contrast, the platelet-to-total cholesterol (PLT-to-total cholesterol) ratio showed a negative correlation with cholesterol concentration (r = -0.63), as did hemoglobin with the platelet-to-hemoglobin (PLT-to-hemoglobin) ratio index (r = -0.34). In addition, the platelet-to-hematocrit ratio (PLT-to-hematocrit) had moderate discriminatory power (AUC: 0.60) balanced in terms of sensitivity (48%) and specificity (80%).

In the fourth study, lower monocyte-to-HDL ratio (MHR) values compared to high MHR values were statistically significantly associated with lower in-hospital mortality (0.9% vs. 5.5%; P < 0.001), mortality at 3 months (4.4% vs. 11.2%; P = 0.02), at 6 months (4.0% vs. 10.2%; P = 0.03), at 1 year (4.2% vs. 10.2%; P < 0.001), and at long-term follow-up (7.5% vs. 13.7%; P < 0.001).

In the fifth study evaluating the diagnostic and prognostic value of cystatin C (CysC) in patients with ACS, CysC levels were significantly higher in patients with acute coronary syndromes compared to controls (MD = 0.36; p < 0.001) and in patients with acute myocardial infarction (AMI) compared to patients with unstable angina (MD = 0.18; p < 0.001). There were no significant differences in CysC levels between patients with STEMI and NSTEMI. Patients who experienced major cardiovascular events (MACE) had higher CysC levels compared to those without such events (MD = 0.25; p < 0.001). In addition, those who survived hospitalization had lower CysC values than patients who died (MD = -0.25; p < 0.001). Elevated CysC concentrations were associated with an increased risk of MACE, cardiac death, total mortality, myocardial reinfarction, and stroke, both during hospitalization and in long-term follow-up.

In study six, galectin-3 (Gal-3) levels were significantly higher in patients with acute coronary syndromes compared to controls (12.84 ± 8.48 ng/mL vs. 7.23 ± 6.05 ng/mL; MD = 3.89; 95% CI: 2.83-4.95; p < 0.001). Also, when comparing patients with acute myocardial infarction to controls, Gal-3 values were significantly elevated (10.09 ± 8.16 vs. 4.64 ± 3.07 ng/mL; MD = 4.30; 95% CI: 0.41-8.18; p < 0.001). Statistical analysis also showed significant differences in Gal-3 levels between STEMI patients and controls (10.62 ± 7.34 vs. 5.54 ± 2.96 ng/mL; MD = 5.54; 95% CI: 3.12-7.97; p < 0.001). In contrast, there were no significant differences between patients with NSTEMI and controls, or between patients with STEMI and NSTEMI.

The seventh study, which aimed to assess the diagnostic value of soluble receptor for urokinase plasminogen activator (suPAR) concentrations in patients with suspected acute coronary syndromes (ACS), showed that mean suPAR concentrations were significantly higher in patients with

ACS compared to controls (3.56 ± 1.38 vs. 2.78 ± 0.54 ng/mL; mean difference: 1.04; 95% confidence interval: 0.64-1.44; $I^2 = 99\%$; $p < 0.001$).

The eighth study, designed to evaluate the usefulness of endocan as a biomarker for differentiating between different forms of acute coronary syndromes, including STEMI, NSTEMI, and UAP, showed that its levels were elevated in the group of patients with STEMI. The mean endocan value in this group was 1.68 (±0.84), which was significantly higher compared to the control group (1.20 ± 0.38; MD = 0.58; 95% CI: 0.10-1.05; p = 0.02). In patients with NSTEMI, the mean endocan concentration was 1.16 (±0.38), which was also slightly higher than in the control group (1.06; MD = 0.17; 95% CI: 0.01-0.33; p = 0.03). However, pooled analysis showed no statistically significant differences in endocan levels between patients with STEMI and those with NSTEMI or UAP, where values were 2.22 (±1.22) and 2.64 (±1.22), respectively (MD = 0.01; 95% CI: -0.20-0.21; p = 0.95).

Conclusions

The studies indicate the important role of selected biomarkers in the diagnosis and prognosis of acute coronary syndromes (ACS). Inflammatory biomarkers play a key role in the risk stratification of patients with ACS. Indicators such as NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), and MHR (monocyte-to-HDL cholesterol ratio) have been shown to be strongly associated with prognosis. Higher values of these parameters correlate with increased risk of cardiovascular complications (MACE) and increased mortality. In addition, platelet indices can aid both the diagnosis and prognosis of ACS. Studies suggest that new parameters, such as platelet to hematocrit ratio and platelet volume indices, may be useful in differentiating STEMI and NSTEMI, which may improve the diagnostic process. Cystatin C is a promising biomarker for assessing the risk of MACE and heart failure. Its elevated levels are associated with a higher risk of death, myocardial infarction, and stroke in patients with ACS, suggesting its potential use in risk stratification and therapeutic decision-making. Patients with ACS exhibit elevated levels of further biomarkers, such as galectin-3 and suPAR, which are markers of chronic inflammation. They may aid early diagnosis and assessment of complication risk, but their routine clinical use requires further research. The role of endocan as a biomarker of endothelial dysfunction is also an important finding. Its levels are markedly higher in patients with ACS, especially in STEMI, suggesting its involvement in atherosclerotic plaque destabilization and coronary artery disease progression. While troponins continue to be the primary diagnostic tool for ACS, the inclusion of additional biomarkers could enhance the accuracy of risk stratification, particularly in patients with unique clinical presentations or comorbidities like chronic kidney disease. In conclusion, most of the studies reviewed point to the need to standardize biomarker thresholds and to develop algorithms that integrate different parameters in ACS risk assessment. Further studies should include a broad spectrum of patients to increase the clinical utility of these indicators and implement them in daily medical practice.