Systemic Biomarkers in Predicting Clinical Outcomes Among Patients with Non-ST Segment Elevation Myocardial Infarction: A Systematic Review

Abstract

Background: The ability to predict clinical outcomes in Non-ST Segment Elevation Myocardial Infarction (NSTEMI) could potentially lead to better risk stratification and treatment management. This systematic review aims to evaluate the predictive value of systemic biomarkers on the clinical outcomes among NSTEMI patients.

Methods: A comprehensive search across PubMed, Web of Science and Scopus was conducted, adhering to PRISMA Statement 2020 guidelines. Original clinical studies involving NSTEMI patients with measured systemic biomarkers were considered. Keyword combinations included the following: 'NSTEMI', 'systemic biomarkers', 'clinical outcomes', 'major adverse cardiac events', and/or 'mortality.

Results: We included 7 studies in total pooling in 863 participants, with biomarkers such as Syntax score, Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Matrix Metallopeptidase 9 (MMP-9), and Perforin (P), among others. All systemic inflammation (SI) biomarkers were found significantly elevated in patients with high Syntax scores. ROC values for major adverse cardiac events (MACE) ranged from 0.592 to 0.637, and for overall mortality from 0.524 to 0.761. Monocytic MMP-9 mRNA levels were found increased in patients with NSTEMI (0.9 +/- 0.3 relative units (RU)). Positive correlations were found between cardiac troponin I plasma concentrations and the frequency of Perforin-positive cells during the first week after the NSTEMI.

Conclusion: Systemic biomarkers, including Syntax score, NLR, PLR, MMP-9, and Perforin, show potential predictive value for clinical outcomes in NSTEMI patients. Their use could aid in early risk stratification and management. However, more large-scale, multicenter studies are warranted to validate these findings.

Keywords: Systemic Biomarkers, Non-ST Segment Elevation Myocardial Infarction, Predictive Value, Risk Stratification, Syntax Score, Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio.

Introduction

Non-ST segment elevation myocardial infarction (NSTEMI) represents a significant portion of acute coronary syndromes, characterized by partial or temporary blockage of the coronary arteries leading to reduced blood flow to the heart (1). While the current standard of care, encompassing risk stratification, antithrombotic therapy, and coronary revascularization, has significantly

improved outcomes, prognosis remains variable and can be influenced by numerous factors, such as patient characteristics, severity of the condition, and timing of intervention (2,3).

One area of clinical interest that has gained considerable traction in recent years is the use of systemic biomarkers for predicting clinical outcomes in NSTEMI patients (4,5). Biomarkers are measurable substances indicative of a biological or pathological process or a response to a therapeutic intervention (6,7). In the context of NSTEMI, biomarkers can provide valuable insight into various facets of the disease process, including the extent of myocardial damage, the presence and degree of inflammation, plaque instability, and the risk of subsequent adverse cardiovascular events (8–11).

Biomarkers such as troponin and C-reactive protein, which are indicative of myocardial injury and inflammation respectively, have been widely used and are well-established in the management of NSTEMI (12). However, these traditional biomarkers may not fully capture the complexity of pathophysiological processes involved in NSTEMI (13). Emerging evidence suggests that other systemic biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), high sensitivity cardiac troponin (hs-cTn), and matrix metalloproteinase-9 (MMP-9), might provide additional predictive value and contribute to a more nuanced understanding of the disease.

Moreover, the discovery of novel biomarkers and the validation of their prognostic value can lead to more personalized care, as the treatment strategy can be tailored to the individual's risk profile. However, the landscape of biomarkers in NSTEMI is rapidly evolving, with numerous studies exploring different markers and their potential role in risk stratification and outcome prediction.

Therefore, it is crucial to systematically review the current evidence on the use of systemic biomarkers in predicting clinical outcomes among NSTEMI patients. This systematic review aims to provide a comprehensive overview of the current state of research, summarizing the main findings and implications for clinical care. It is hoped that this effort will shed light on the potential of these markers in guiding clinical decision-making in the management of NSTEMI patients, while also highlighting gaps in our understanding and providing directions for future research.

Methods

In line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 guidelines (14), we designed the methodology for this systematic review. The primary objective is to critically assess literature, highlighting the predictive utility of systemic biomarkers in forecasting clinical outcomes among NSTEMI patients.

Research Question

This systematic review aims to answer the following research question: How well do systemic biomarkers predict clinical outcomes in NSTEMI patients?

PICO Framework

The PICO (Population, Intervention, Comparison, Outcome) model for this review is defined as follows:

- Population: Patients diagnosed with Non-ST Segment Elevation Myocardial Infarction (NSTEMI)
- Intervention: Assessment of systemic biomarkers
- Comparison: NSTEMI patients lacking these biomarkers
- Outcome: Determination of clinical outcomes, including major adverse cardiac events and mortality

Search Methodology

To include the most relevant and current research findings, we performed a comprehensive literature search across three databases: PubMed, Scopus, and Web of Science. For the search, we used a combination of keywords and MeSH terms including 'NSTEMI', 'systemic biomarkers', 'clinical outcomes', 'major adverse cardiac events', and/or 'mortality.' We did not restrict the search based on publication date, language, or geographical location and solely included peer-reviewed articles.

Article Selection

Titles and abstracts of articles retrieved from the initial search were independently assessed by two reviewers for relevance to the study of systemic biomarkers and their correlation with NSTEMI outcomes. Any disagreements between reviewers were resolved through mutual discussion, and if necessary, a third reviewer was consulted. We procured the full texts of relevant articles for a thorough review. Studies that met the following criteria were included: original research articles without time limitations, focused on systemic biomarkers' role in predicting NSTEMI outcomes, and provided adequate data for extraction and subsequent analysis.

Data Synthesis and Analysis

The research team systematically extracted data from selected studies, which included author names, publication year, study design, biomarkers under study, characteristics of the study population, main results, and implications for care. We then qualitatively synthesized and analyzed the extracted data. This process allowed us to compile and summarize the key findings, offering an overview of the role of systemic biomarkers in predicting NSTEMI outcomes.

Results

Of the 327 studies identified from the databases, 13 duplicates were removed. In the screening phase, 314 studies were assessed for titles and abstracts, of which 56 were retrieved for full-text eligibility. Finally, 7 studies were included in this systematic review (**Figure 1**).

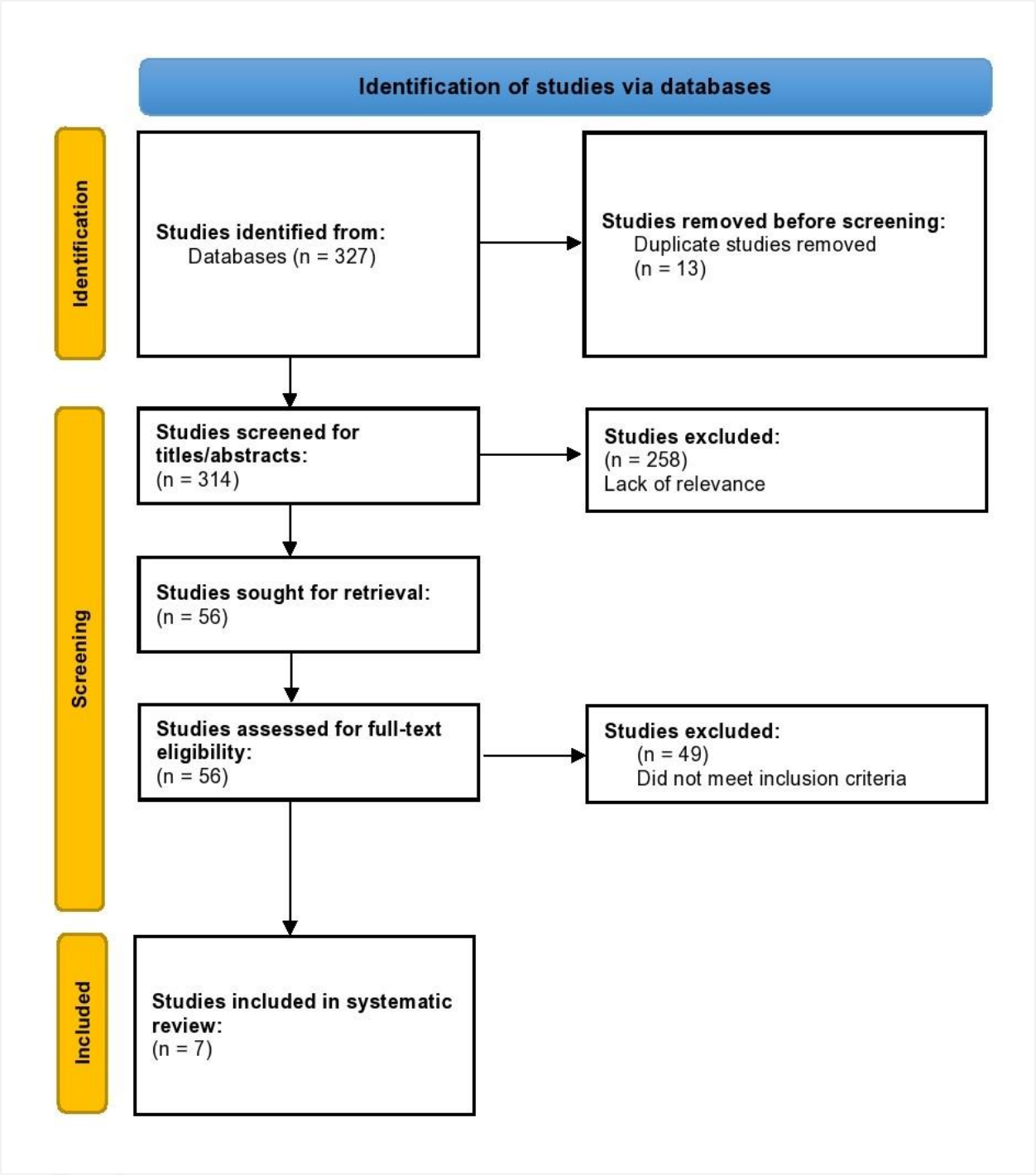

Figure 1. PRISMA Flowchart Depicting the Study Selection Process.

The characteristics of the included studies (N=7) are listed in Table 1.

Table 1. Characteristics of Included Studies.

Author, Year	Title	Study Design	Population Characteristics	Biomarkers Reported	Main Findings	Implications for Care

Li, 2023 (15)	Comparison of Different Systemic Inflammatory Markers in Predicting Clinical Outcomes with Syntax Score in Patients with Non-ST Segment Elevation Myocardial Infarction: A Retrospective Study	Retrospective study	429 patients with NSTEMI	Syntax score, NLR, PLR, hsCAR, SII	All SI biomarkers were significantly higher in patients with high Syntax scores, and were independent risk factors of 6-month MACE, with ROC values for MACE (0.637, 0.592, 0.631, 0.59 respectively) and for over-all mortality (0.53, 0.524, 0.761, 0.553 respectively)	The SI biomarkers could offer better risk stratification than the Syntax score for NSTEMI patients
Nishiguchi, 2016 (16)	Local Matrix Metalloproteinase 9 Level Determines Early Clinical Presentation of ST-Segment-Elevation Myocardial Infarction	Cross-sectional study	111 patients with MI (n=94) and stable angina pectoris (n=17)	MMP-9, Myeloperoxidase	Local MMP-9 levels were significantly higher than systemic levels. Poststent local MMP-9 level was significantly elevated in patients with STEMI (109.9 [54.5-197.8] ng/mL) versus non-STEMI: 52.9 [33.0-79.5] ng/mL; stable angina pectoris, 28.3 [14.2-40.0] ng/mL; $P < 0.01$	High MMP-9 levels may predict STEMI and require additional attention
Joshi, 2015 (17)	Systemic Atherosclerotic Inflammation Following Acute Myocardial Infarction: Myocardial Infarction Begets Myocardial Infarction	Observational study	40 patients with MI and 40 with stable angina	Troponin, C-reactive protein, 18F-fluorodeoxyglucose	MI patients had higher aortic 18F-fluorodeoxyglucose uptake (tissue-to-background ratio 2.15 ± 0.3 versus 1.84 ± 0.18, $P < 0.0001$) and plasma C-reactive protein	Larger infarcts can accelerate systemic atherosclerosis and require early interventions

					concentrations (6.5 [2 to 12.75] versus 2 [0.5 to 4] mg/dL, P = 0.0005). Peak plasma troponin concentrations correlated with aortic 18F-fluorodeoxyglucose uptake (r = 0.43, P = 0.01)	
Laskarin, 2011 (18)	Perforin-mediated cytotoxicity in non-ST elevation myocardial infarction	Observational study	48 patients with NSTEMI	Perforin (P)	Positive correlations were found between cardiac troponin I plasma concentrations and the frequency of P(+) cells, P(+) T cells, P(+) NK cells and their CD56(+dim) and CD56(+bright) subsets during the first week after the NSTEMI	Strong and prolonged P-mediated systemic inflammatory reaction may sustain autoaggressive reactions towards myocardial tissue in NSTEMI
Brunner, 2010 (19)	Relation of matrix metalloproteinase-9/tissue inhibitor of metalloproteinase-1 ratio in peripheral circulating CD14+ monocytes to progression of coronary artery disease	Cross-sectional study	66 patients with various stages of coronary artery disease and 16 healthy controls	MMP-9, TIMP-1	Monocytic MMP-9 mRNA levels were increased in those with UAP/NSTEMI (0.9 +/- 0.3 relative units (RU), P < 0.001), STEMI (0.8 +/- 0.4 RU, P < 0.001) and SAP (0.7 +/- 0.3 RU, P < 0.01), compared with controls (0.4 +/- 0.1 RU)	The MMP-9/TIMP-1 ratio could be used as a potential marker for the progression of coronary artery disease
Ferrante, 2010 (20)	High levels of systemic myeloperoxidase are associated with coronary plaque erosion	Observational study	25 patients with acute coronary syndromes	Myeloperoxidase, C-reactive protein	The levels of myeloperoxidase were significantly higher in patients with eroded (n=14)	Elevated myeloperoxidase levels may indicate increased risk of eroded plaque

	in patients with acute coronary syndromes: a clinicopathological study				versus ruptured plaques (n=11): median 16.7 (IQR 9.5 to 23.8) versus 7.9 (4.7 to 12.3) ng/mL; P = 0.013	
Mangina s, 2005 (21)	Peripheral levels of matrix metalloproteinase-9, interleukin-6, and C-reactive protein are elevated in patients with acute coronary syndromes: correlations with serum troponin I	Cross-sectional study	88 patients with unstable angina, NSTEMI, and stable coronary artery disease	MMP-9, TIMP-1, CRP, IL-6, Troponin-I	Patients with ACS had significantly higher plasma levels of MMP-9 (529 ± 282 vs 402 ± 192 ng/ml, P = 0.01), CRP (2.4 ± 2.6 vs 1.1 ± 0.9 mg/dl, P = 0.003), and IL-6 (9.2 ± 11.6 vs 3.5 ± 2.7 pg/ml, P = 0.0007) than patients with stable angina	Elevated MMP-9, CRP, and IL-6 levels could indicate an increased risk of ACS

Abbreviations: ACS: Acute Coronary Syndromes; CRP: C-Reactive Protein; hsCAR: High-Sensitivity C-Reactive Protein; IQR: Interquartile Range; IL-6: Interleukin-6; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; MMP-9: Matrix Metallopeptidase 9; NLR: Neutrophil-to-Lymphocyte Ratio; NSTEMI: Non-ST Segment Elevation Myocardial Infarction; P: Perforin; PLR: Platelet-to-Lymphocyte Ratio; ROC: Receiver Operating Characteristic; RU: Relative Units; SAP: Stable Angina Pectoris; SII: Systemic Immune-Inflammation Index; STEMI: ST Segment Elevation Myocardial Infarction; TIMP-1: Tissue Inhibitor of Metalloproteinases 1; UAP: Unstable Angina Pectoris; 18F-fluorodeoxyglucose: Fluorodeoxyglucose (FDG) Positron Emission Tomography; Syntax score: A scoring system used to grade the complexity of coronary artery disease.

In a retrospective study by Li et al. (2023), involving 429 patients with NSTEMI, they reported systemic inflammation (SI) biomarkers, including Syntax score, NLR, PLR, hsCAR, and SII (15). These biomarkers were significantly higher in patients with elevated Syntax scores, proving to be independent risk factors of 6-month MACE, with ROC values for MACE (0.637, 0.592, 0.631, 0.59 respectively) and for overall mortality (0.53, 0.524, 0.761, 0.553 respectively). This research suggests that these SI biomarkers may offer more comprehensive risk stratification than the Syntax score for NSTEMI patients.

In 2016, Nishiguchi et al. conducted a cross-sectional study with 111 patients with MI and stable angina pectoris (16). They reported that local MMP-9 levels were significantly higher than systemic levels. Additionally, post-stent local MMP-9 levels were significantly elevated in patients with STEMI (109.9 [54.5-197.8] ng/mL) compared to non-STEMI (52.9 [33.0-79.5] ng/mL) and

stable angina pectoris (28.3 [14.2-40.0] ng/mL; P < 0.01). The study suggests that high MMP-9 levels may predict STEMI and necessitate additional attention.

Joshi et al., in their 2015 observational study involving 40 patients with MI and 40 with stable angina, showed that MI patients had higher aortic 18F-fluorodeoxyglucose uptake (tissue-to-background ratio 2.15 ± 0.3 vs 1.84 ± 0.18, P < 0.0001) and plasma C-reactive protein concentrations (6.5 [2 to 12.75] vs 2 [0.5 to 4] mg/dL, P = 0.0005) (17). The peak plasma troponin concentrations correlated with aortic 18F-fluorodeoxyglucose uptake (r = 0.43, P = 0.01), implying that larger infarcts can accelerate systemic atherosclerosis and necessitate early interventions.

A 2011 observational study by Laskarin et al., focused on 48 patients with NSTEMI and the biomarker Perforin (P) (18). They found positive correlations between cardiac troponin I plasma concentrations and the frequency of P(+) cells, P(+) T cells, P(+) NK cells, and their CD56(+dim) and CD56(+bright) subsets during the first week after NSTEMI. These findings hint that a strong and sustained P-mediated systemic inflammatory reaction might induce autoaggressive reactions towards myocardial tissue in NSTEMI patients.

Brunner et al. (2010) performed a cross-sectional study with 66 patients at different stages of coronary artery disease and 16 healthy controls (19). They discovered that monocytic MMP-9 mRNA levels were increased in patients with UAP/NSTEMI (0.9 +/- 0.3 relative units (RU), P < 0.001), STEMI (0.8 +/- 0.4 RU, P < 0.001), and SAP (0.7 +/- 0.3 RU, P < 0.01) compared to controls (0.4 +/- 0.1 RU). They proposed that the MMP-9/TIMP-1 ratio could be used as a potential marker for the progression of coronary artery disease.

Ferrante et al. (2010), in their observational study involving 25 patients with acute coronary syndromes, found that the levels of myeloperoxidase were significantly higher in patients with eroded plaques (n=14) versus ruptured plaques (n=11): median 16.7 (IQR 9.5 to 23.8) versus 7.9 (4.7 to 12.3) ng/mL; P = 0.013 (20). This finding suggests that elevated myeloperoxidase levels may indicate an increased risk of eroded plaque.

In a 2005 cross-sectional study by Manginas et al., involving 88 patients with unstable angina, NSTEMI, and stable coronary artery disease, it was found that patients with ACS had significantly higher plasma levels of MMP-9 (529 ± 282 vs 402 ± 192 ng/ml, P = 0.01), CRP (2.4 ± 2.6 vs 1.1 ± 0.9 mg/dl, P = 0.003), and IL-6 (9.2 ± 11.6 vs 3.5 ± 2.7 pg/ml, P = 0.0007) than patients with stable angina (21). They concluded that elevated MMP-9, CRP, and IL-6 levels could signal an increased risk of ACS.

Discussion

From the body of research presented, it becomes clear that biomarkers hold considerable predictive value in the clinical outcomes among patients with non-ST segment elevation myocardial infarction (NSTEMI). Various studies have highlighted how different biomarkers, including Syntax score, NLR, PLR, hsCAR, SII, MMP-9, troponin, C-reactive protein, 18F-fluorodeoxyglucose, and Perforin, among others, can play pivotal roles in risk stratification and diagnosis.

The study by Li et al. suggested that systemic inflammation biomarkers may provide better risk stratification than the Syntax score for NSTEMI patients (15). Similarly, research by Nishiguchi et al. posited that MMP-9 could predict STEMI and necessitate additional attention (16), while Joshi et al. highlighted the correlation of peak plasma troponin concentrations with aortic 18F-fluorodeoxyglucose uptake, which could accelerate systemic atherosclerosis (17). Laskarin et al. identified the role of Perforin in NSTEMI, suggesting a systemic inflammatory reaction that might incite autoaggressive reactions towards myocardial tissue (18). Meanwhile, studies by Brunner et al. and Manginas et al. proposed the use of the MMP-9/TIMP-1 ratio and elevated levels of MMP-9, CRP, and IL-6 as potential markers for the progression of coronary artery disease and an increased risk of ACS, respectively (19,21).

Various biomarkers have been identified and studied for their role in predicting clinical outcomes among patients with NSTEMI. For instance, Giannitsis et al. (2013) discussed the relevance of cardiac troponin T and I as essential biomarkers in patients with NSTEMI (22). They highlighted their critical role in diagnosis, risk stratification, and guide to therapy. In a study conducted by Ranjith et al. (2017), biomarkers such as C-reactive protein, fibrinogen, and interleukin-6 were discussed as valuable prognostic markers in patients with NSTEMI (23). They concluded that these biomarkers contribute to predicting the likelihood of future cardiovascular events and guide therapeutic interventions.

Novel biomarkers such as the soluble suppression of tumorigenicity-2 (sST2) and galectin-3 have also been examined in the context of NSTEMI. Saunders et al. (2016) in their study discussed the potential of these new biomarkers in providing incremental prognostic information in NSTEMI patients (24). A study by Widera et al. (2012) found that elevated levels of growth-differentiation factor-15 (GDF-15) were associated with an increased risk of mortality among NSTEMI patients (25). MMP-9 is another promising biomarker studied extensively in NSTEMI patients. A study by Dhingra et al. (2017) found that higher MMP-9 levels were significantly associated with adverse outcomes in NSTEMI patients (26).

The studies highlighted in this review highlight the potential of specific biomarkers in managing, treating, and predicting outcomes in patients with NSTEMI. Each biomarker, as indicated by these studies, has a unique function and correlation with different disease aspects. Therefore, understanding these biomarkers and their roles can provide invaluable insight for improving clinical practice and patient outcomes. However, more prospective studies and trials are needed to further confirm these associations and explore additional biomarkers that can help guide diagnosis and treatment strategies for NSTEMI patients.

Limitations and Strengths

While this systematic review provides valuable insights into the role of systemic biomarkers in predicting clinical outcomes in NSTEMI patients, certain limitations exist. The studies included in this review varied considerably in their design, methodology, patient cohorts, and reported outcomes, which could limit the generalizability of our findings. Most of the studies were observational in nature, which may be prone to selection bias and residual confounding.

Additionally, the biomarkers studied in the included articles were diverse, and this heterogeneity might have affected the overall interpretation and conclusions of the review.

This study's primary strength is its comprehensive and in-depth examination of a diverse range of biomarkers, from traditional ones such as troponin and C-reactive protein to more novel ones such as MMP-9, Syntax score, and hsCAR. Moreover, the inclusion of studies with various designs and diverse patient cohorts enhances the generalizability of our findings. The rigorous methodology used in this review also ensures the validity and reliability of the findings.

Recommendations

Based on the findings of this review, we recommend that future research should focus on the evaluation of novel biomarkers and their role in clinical outcomes among NSTEMI patients. It would be beneficial to conduct more prospective and randomized trials to minimize bias and confounding. Multi-center studies with larger sample sizes could also enhance the power and generalizability of the results. Further, the combination of several biomarkers could be explored as a potential strategy for improving the prediction of clinical outcomes in NSTEMI patients.

Conclusion

Our systematic review comprehensively analyzed a wide range of biomarkers and their predictive utility for clinical outcomes among patients with NSTEMI. The results highlighted several promising biomarkers, such as the Syntax score, MMP-9, and hsCAR, which were associated with major adverse cardiac events and mortality in these patients. These findings emphasize the potential of these biomarkers in guiding therapeutic decision-making and risk stratification in NSTEMI patients. However, given the heterogeneity in the studies and biomarkers analyzed, there is a need for more focused and large-scale studies to validate these findings further and explore the potential of other emerging biomarkers. Moreover, given the complex pathophysiology of NSTEMI, a combination of biomarkers might offer a more precise prediction of clinical outcomes. The incorporation of these biomarkers into clinical practice could significantly enhance the management of NSTEMI patients, leading to better patient outcomes.

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