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Novel Emerging Inflammatory Biomarkers Predict the Coronary Artery Diseases-Related Complications: An Integrative Review

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ABSTRACT

This integrative Review aims to evaluate the utility of novel emerging inflammatory biomarkers in predicting major adverse cardiac events (MACEs) in patients with acute coronary artery disease (CAD). Cardiovascular diseases (CVDs), primarily driven by myocardial ischemia due to atherosclerosis, are the leading cause of global morbidity and mortality. Traditional biomarkers have offered mixed prognostic capabilities, necessitating the exploration of new markers that encompass complete blood count (CBC) parameters and CBC-derived indices. We conducted a comprehensive review, following PRISMA guidelines, and searched databases such as PubMed, Web of Science, ERIC, and Science Direct up to May 2023, focusing on inflammatory indices and their correlation with cardiovascular outcomes. The selected studies, published within the last five years and meeting our inclusion criteria, provided data on various biomarkers including Platelet Distribution Width (PDW), Mean Reticulocyte Volume, and systemic inflammatory indices such as Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR). Emerging indices like the Systemic Inflammatory Index (SII) demonstrated significant predictive power for both short-term and long-term cardiovascular complications. Our findings suggest that these novel biomarkers, particularly CBC-derived indices, offer valuable prognostic information that could enhance clinical decision-making in managing coronary artery disease. Further research and standardization are required to fully integrate these biomarkers into routine clinical practice.

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Introduction

Background

Cardiovascular diseases (CVDs) are the leading cause of death in the world and is very often caused by myocardial ischemia due to the development and progression of atherosclerosis. Coronary artery disease (CAD) remains a significant cause of mortality and morbidity and it includes acute coronary syndromes (ACS); such as myocardial infarction (MI), unstable angina (UA), and chronic coronary syndromes. Coronary artery disease may result in heart failure (HF) and is associated with poor clinical outcome [1]. In order to better assess the risk for poor cardiovascular (CV) outcomes, many humoral parameters have been investigated over the years as potential biomarkers for prognosis, with mixed results. Although progress has been made and some parameters proved to be sufficiently reliable for this purpose, the perfect biomarker has not been found.

Numerous pathophysiological factors, including as immunological mechanisms, inflammation, and thus all significant subtypes of circulating blood cells, contribute to atherosclerosis, plaque blockage, and the development of ACS. The development of plaques and the prevalence of ACS are influenced by platelets. The first blood cells to enter the damaged myocardium are neutrophils. Monocytes are also involved in the development of plaques and are essential for the healing of myocardial damage and the subsequent remodeling of the heart, whereas lymphocytes are well-known for mediating immune responses and inflammatory processes [2].

Due to their accessibility and dependability as CVD biomarkers, research has increasingly concentrated on complete blood count (CBC) parameters alone, CBC-derived indices, and other blood cell-related studies [3].

Aim

This review aims to assess the utility of the novel emerging biomarkers in estimating the major adverse cardiac events for both short and long-term of patients with acute coronary artery diseases.

Method

The study followed the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) checklist reporting guidelines [4]. The flow chart of the whole study is shown in Figure 1.

Search Strategies

For the purpose of the current work, we conducted a comprehensive review of the inflammatory biomarkers (conventional & emerging) as indices and their association with the outcomes of cardiovascular diseases. Bibliographical searches were performed in the (PubMed, Web of Science, ERIC, Science direct) databases up to May 24, 2023, using the following key words: Hematological indices, Inflammatory indices, coronary artery diseases or CAD,

Cardiovascular diseases or CVD, Major Adverse Cardiac Events or MACEs, outcomes and complications, Systemic Inflammatory Index or SII.

Our search yielded a net of 15 articles as included after meeting the inclusion criteria: not older than 5 years (since 2019), written in English language, and MACEs-outcomes-related, and exclusion of systematic and scooping reviews. In addition, references included in the articles were searched to identify any possible eligible original research (Figure 1).

Data Extraction

The data were independently extracted by two investigators and re-checked by the other two authors using a table with the following data: Biomarker, Details, Outcomes, Follow-Up, sample size (n), predictor/Cut-Off Value, and Reference.

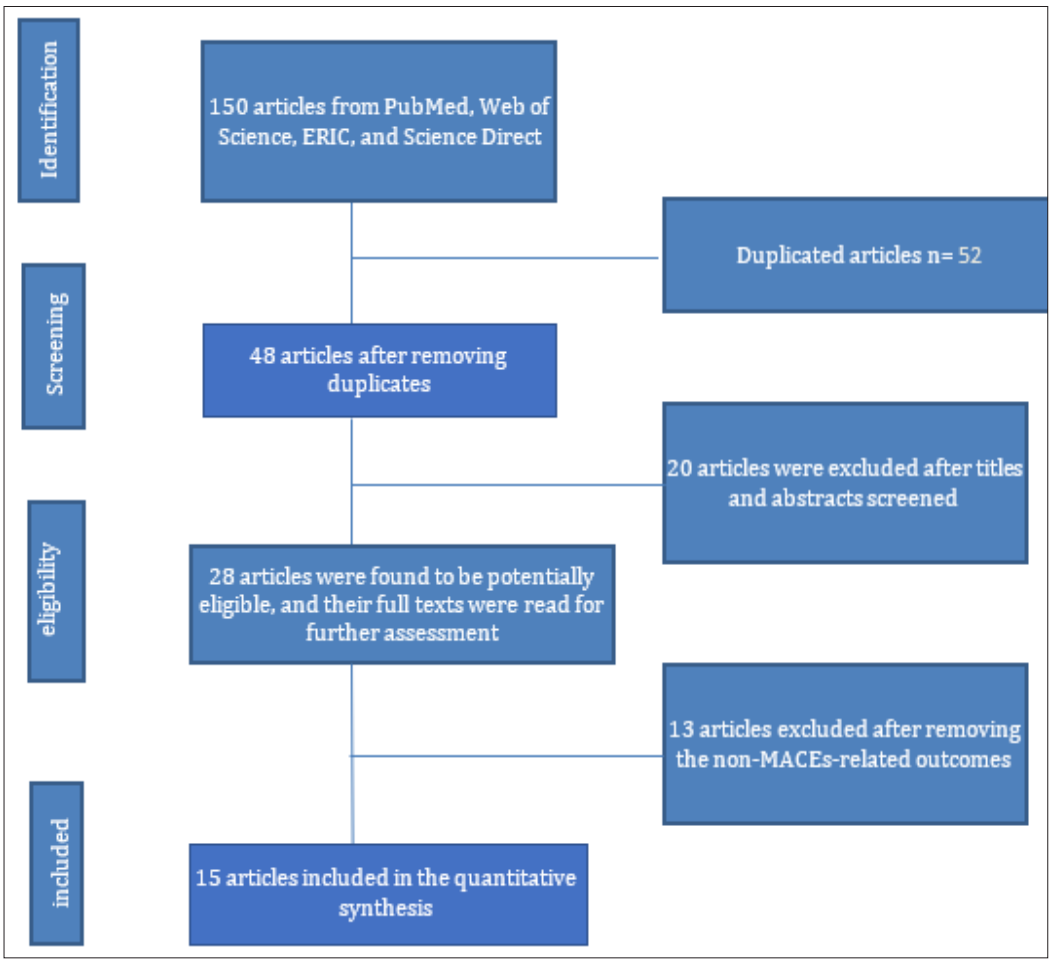

Figure 1: Flowchart for Selection of Published Eligible Studies for the Review

Results

In this part, the results will be discussed into two main sections: CBC parameters and CBC-derived indices. The latest will be discussed under three main headings: conventional biomarkers, novel emerging biomarkers, and conventional vs. novel emerging biomarkers.

CBC Parameters

It was discovered that some platelet and red blood cell characteristics had predictive value for HF and death. Platelet distribution width (PDW) was independently linked with both systolic HF and one-year mortality, according to a Polish retrospective observational analysis of 278 patients having at least one stent implant for ACS. A PDW value > 12.8% could predict the incidence of 1-year HF with LVEF 35% following ACS treated with primary PCI (AUC 0.614, 81% sensitivity, 39% specificity, p = 0.0177); this is in accordance with ROC analysis [5].

Mean reticulocyte volume (fL) was found to be a unique biomarker of incident heart failure over a median follow-up of 6.2 years in a large biobank investigation involving 500,451 UK citizens [6]. Higher red cell distribution width (RDW) and lower mean corpuscular hemoglobin concentration (MCHC) were each independently related with all-cause mortalities over a follow-up period of 2.2 years, according to a study of 443 patients with acute heart failure with preserved ejection fraction (HFPEF) [7].

CBC-Derived Indices

Conventional Biomarkers

In this section, the conventional biomarkers will be discussed including Platelet-to-Hemoglobin Ratio (PHR), Monocyte to HDL-cholesterol Ratio (MHR), Red cell Distribution Width (RDW), Mean Corpuscular Hemoglobin Concentration (MCHC), Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Inflammatory Index (SII) as a novel emerging biomarker(Table 1).

The neutrophil to lymphocyte ratio (NLR) at admission and absolute NLR trajectory throughout hospitalization were both independently related with all-cause death, according to [7]. In addition, all-cause mortality was linked to High platelet to hemoglobin ratio (PHR) over a median follow-up of 5.2 years, according to study findings on 2599 patients with CAD complicated by congestive heart failure. The risk of all-cause mortality was shown to be higher in patients in the highest quartile of PHR compared to those in the lowest quartile [8].

In a trial of 231 patients admitted with STEMI for the first time who received primary PCI in the first 12 hours, a combined monocyte to HDL-cholesterol ratio (MHR) was also discovered to have prognostic value. Patients who had negative cardiac remodeling at the 6-month follow-up had greater MHR at the time of admission [9]. Only MHR remained significant in multivariate analysis, despite the fact that multiple hematological markers and indices at admission were strongly related with unfavorable cardiac remodeling in univariate analysis. With a threshold of 1.6, MHR outperformed other indices in terms of predicting unfavorable cardiac remodeling: 92.7% sensitivity, 70.1% specificity, AUC of 0.84 [0.78-0.88], positive predictive value of 46.8%, negative predictive value of 96.7%, p 0.001. MHR values greater than 1.6 also predicted all-causes mortalities [9].

Table 1: Conventional Biomarkers

Biomarker	Details	Outcome(s)	Follow-Up	n	Predictor/Cut-Off Value	Reference
PHR	Undergoing CAG; diagnosis: CAD with CHF	All-cause mortality	5.2 years	2599	≥1.69	[8]
MHR	First STEMI + PCI		1.5 years	231	>1.6 Higher	[9]
RDW	Hospitalization with acute HFpEF	All-cause mortality	2.2 years	443	Higher	[7]
MCHC					lower	
NLR on admission					Higher	
NLR trajectory					Higher	

Abbreviations: CAG, coronary artery graph; CAD, coronary artery disease; STEMI, ST elevation myocardial infarction; CHF, congestive heart failure; PCI, percutaneous coronary intervention; HFpEF, heart failure with preserved ejection fraction; NLR, normocyte-to-lymphocyte ratio; RDW, red cell distribution width, MCHC, Mean corpuscular hemoglobin concentration; MHR, maximum heart rate; PHR, platelet-to-hemoglobin ratio.

Novel Emerging Biomarkers

In this section the novel emerging biomarkers will be discussed including Systemic Inflammatory Index (SII) where it is calculated as Platelet Count x Neutrophil Count/Lymphocyte count, Systemic Inflammatory Response Index (SIRI) Where it is calculated as Monocyte Count x Neutrophil Count/Lymphocyte count, and Systemic Immune-Inflammation Response Index (SIIRI) where it is calculated as Platelet Count x Monocyte Count x Neutrophil Count/Lymphocyte count (Table 2).

In another study that evaluated the effectiveness of SII in predicting the long-term prognosis of 711 elderly patients (aged 65 to 85) with acute myocardial infarction (AMI) who underwent percutaneous coronary intervention (PCI). All-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE) both in-hospital and over a three-year follow-up period were the clinical objectives [10]. According to the Kaplan-Meier analysis, patients with greater SII scores had worse survival rates, which also predicted in-hospital and long-term (<3 years) outcomes. In multivariate analyses, SII demonstrated an independent value for predicting in-hospital mortality (hazard ratio (HR), 3.32; 95% confidence interval (CI), 1.55-7.10; p0.01), in-hospital MACCE (HR, 1.43; 95%CI, 1.02-2.00; p=0.04), long-term mortality (HR, 1.95; 95%CI, 1.23-3.09; p0.01), as well as long-term MACCE (E (HR, 1.72; 95%CI, 1.23–2.40; p<0.01) [11].

A cohort prospective analysis included 5602 CAD patients who underwent percutaneous coronary intervention (PCI) operations between 2005 and 2015. Total peripheral platelet count (P)* neutrophil-to-lymphocyte ratio (N/L) were used to calculate the systemic immune-inflammation index (SII). SII had a 694.3 109 /L cut-off value for major cardiovascular events (MACE). The results of both univariate and multivariate analyses revealed that a higher SII score (694.3) was independently associated with an increased risk of developing cardiac death (HR: 2.02; 95% CI: 1.43-2.86), nonfatal MI (HR: 1.42; 95% CI: 1.09-1.85), nonfatal stroke (HR: 1.96; 95% CI: 1.28-2.99), MACE (HR: 1.65; 95% CI: 1.36-2) [12].

In a prospective study, aimed to assess the association of SII, SIRI with all-cause mortality and cardiovascular mortality in the National Health and Nutrition Examination Survey (NHANES) [13]. 42,875 adults who were free of pregnancy, CVDs (stroke, acute coronary syndrome), cancers were evaluated over the period of 1994-2018. The mean age of individuals were 44 ± 18 years, during the follow-up period, 4250 deaths occurred, including 998 deaths from CVDs.

Adults with SII levels >655.56 had greater all-cause mortality (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.18-1.41) and cardiovascular mortality (HR, 1.33; 95% CI, 1.11-1.59) than those with SII levels 335.36, according to Cox proportional hazards modeling. Adults with SIRI levels >1.43 were more likely than adults with SIRI levels 0.68 to die from all causes (HR, 1.39; 95% CI, 1.26-1.52) and cardiovascular disease (HR, 1.39; 95% CI, 1.14-1.68). Elevated SII or SIRI levels in the general population of those over 60 were linked to an increased risk of mortality from all causes [13].

In a study conducted by Tang, and colleagues where they aimed to clarify the potential predictive significance of SII in a assessing the poor prognosis of critically ill patients with CHF, the results showed that high level of SII was independently associated with 30- and 90- day and hospital mortalities (tertile 3 vs. tertile 1: HR, 95% CIs: 1.23, 1.04-1.45; 1.21, 1.06-1.39; 1.26, 1.05-1.50) and the incidence of MACEs (tertile 3 vs. tertile 1: OR, 95% Cl: 1.39, 1.12-1.73) in critically ill patients with CH, but no significant correlation was found between Sll and the readmission rate [10]. Consistently, patients with high SII level still presented a significantly higher short-term mortality than patients with low SII in the PSM subset. In conclusion, in critically ill patients with CHF, high level of SII could effectively predict high 30- and 90-day and hospital mortalities, as well as the high risk of occurrence of MACEs [10].

The systemic inflammatory response index (SIRI) was assessed for its ability to predict (MACE), which includes overall death, nonfatal myocardial infarction, nonfatal stroke, and unscheduled repeat revascularization (URR). 355 of the 1724 ACS patients who underwent PCI between 2016 and 2017 were found to have MACE. The findings demonstrated a statistically significant relationship between SIRI and MACE (hazard ratio: 1.127; 95% confidence interval: 1.034–1.229; p =.007). Patients with greater SIRI classes had a higher cumulative incidence of overall death (p .001), non-fatal MI (p 14.004), non-fatal stroke (p 14.028), and URR (p .001) when taking into account each component of MACE [14].

An extended, unique systemic immune-inflammation response index (SIIRI) was developed, which is determined by the peripheral neutrophil, monocyte, platelet, and lymphocyte counts. It was evaluated over 240 individuals with acute coronary syndrome who later underwent percutaneous coronary intervention in India. Laboratory assessments including cell counts and the SYNTAX score was used to assess the severity of CAD. The study found that SIIRI was a standalone predictor of severe CAD on multivariate analysis, with an adjusted odds ratio (OR) of 1.666 [1.376- 2.017] every 105-unit increase. Comparing the SII, SIRI neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio, and platelet-lymphocyte ratio, the SIIRI exhibited the largest area under the receiver operator curve (.771 [.709-.833]). The best cut-off for SIIRI was 4.3 × 105, with sensitivity = 69.9% and specificity = 75.8% [15].

Table 2: Novel Emerging Biomarkers

Biomarker	Details	Outcome(s)	Follow-Up	n	Predictor/Cut-Off Value	Reference
SIIRI	ACS +PCI	CAD severity	N/A	240	SIIRI 4.3 × 105, sensitivity = 69.9%, specificity = 75.8%	[15]
SII	AMI+PCI	all-cause mortality MACCE	3 years	711	Higher	[10]
SII	Free of pregnancy, CVDs, and cancer	all-cause mortality Cardiovascular mortality	20 years	42,875	SII levels >655.56	[13]
SIRI					SIRI levels >1.43	[13]
SII	Poor prognosis of CHF	30-day & 90-day and All-cause mortality (Primary) Readmission rate And Occurrence of MACE (Secondary)	N/A	4606	Higher with short-term mortality 878.06*103 with 97.6% sensitivity, 91% specificity	[10]
SII	CAD+PCI	MACE	54.6±35.1 months	5602	694.3 109 /L	[12]
SIRI	ACS+PCI		927 days	1724	Higher	[14]

Abbreviations: SIIRI, systemic immune-inflammatory response index; SII, systemic inflammatory index; SIRI, systemic inflammatory response index; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CAD, coronary artery disease; AMI, acute myocardial infarction; CVDs, cardiovascular diseases; MACCE, major adverse cardiac and cerebrovascular events; CHF, congestive heart failure; MACE, major adverse cardiac event.

Conventional Biomarkers Vs. Novel Emerging Biomarkers

In this section, we will discuss the conventional biomarkers that have already discussed earlier with the novel emerging biomarkers which just discussed just before this section (Table 3). In a retrospective observational study involving 843 individuals with STEMI, aimed to evaluate the prediction power of SII, NLR, and PLR and MACE. higher SII was linked to cardiac death, non-fatal MI, non-fatal stroke, congestive HF necessitating hospitalization, and revascularization procedures (PCI or coronary artery bypass graft—CABG). Using a SII cut-off value of 951.7, the ROC analysis showed that MACE could be predicted with 64.6% sensitivity and 73.6% specificity (AUC 0.741, p 0.0001), and the three-variable SII outperformed its two-variable competitors, NLR and PLR, in terms of predictive value [16].

Dolu and colleagues conducted a study to evaluate the relationship between intracoronary thrombus burden and SII, and to compare the predictive capacity of SII together with NLR and PLR in patients with STEMI who underwent PCI [17]. The study found that High NLR (OR: 1.068, 95% Cl:1.023-1.404; p = 0.031), PLR (OR: 1.012, 95% C1.002-1.018; p = 0.043), SIOR: 1.325, 95% Cl: 1.156-1.879; p = 0.015) and low left ventricle ejection fraction (LVEF) (OR: 0.957, 95% Cl:0.924-0.990; p = 0.012) were found to be independent predictors of high thrombus burden [17].The SII values above 812 predicted a high thrombus burden with a sensitivity of 82% and specificity of 73% (AUC: 0.836; 95% C1:0.795-0.877; p < 0.001). This predictive-ness of SII was stronger as compared to NLR (0.836 vs. 0.818, p = 0.043) and PLR (0.836 vs. 0.780, p < 0.001).

The SII is an independent predictor of high thrombus burden in patients with STEMI and it is superior to NLR and PLR in this regard [17] In a retrospective, single-center study where it investigated the role of hematological indices (NLR, PLR, SII) in predicting the short-term outcomes after off-pump coronary artery bypass grafting that included 1007 patients [18]. About 20% (205) of the patients manifested poor postoperative outcomes such as MACE, duration of mechanical ventilator more than 24 hours, new-onset renal failure, sepsis and death. NLR, PLR and SII significantly predicted those poor outcomes, but the SII showed significant positive correlation with all measured outcomes.

The result of this study found that age, WBC, CRP and SII were found to be co-independent predictors of MACE in both the whole population and in patients with STEMI and NSTEMI. The SII level showed superior diagnostic performance than WBC, CRP, NLR and PLR in predicting MACE in the whole population. MACE risk was 48.7 times higher in those with SII level > 955.8 compared to those with a level 955.8. The predictive value of SII level in predicting MACE in STEMI patients were found to be > 916.7, with 82.9% sensitivity and 83.2% specificity, and MACE risk was found to be 24.6 times higher in patients with SII level > 916.7 compared to those with a level ≤ 916.7 (HR: 24.6; 95% CI = 14.4–42.1; p < 0.001) [18].

In a study where they aimed to examine and contrast the ability of a systemic immune inflammation index (SII) to predict MACCEs that occurred one year after carotid artery stenting (CAS) in patients with established CAD with 157 patients who underwent CAS for 5-year retrospectively, they ended up that Compared with other inflammatory parameters evaluated in the study including C-reactive protein, platelets, and PLR, SII had a better and adequate discriminatory performance for MACCEs (area under the curve: 0.762, p<0.001). An SII ≥615 predicted the one-year MACCEs with 81% sensitivity and 63% specificity [19].

Another study where 395 patients who underwent coronary angiography were enrolled and have been divided into two groups; 285 were included in the CAD group and the 110 remaining in the non-CAD group. The study investigated the association between the SII and the severity of CAD. The results revealed that the SII is an independent risk factor for the occurrence and severity of CAD in comparing to the NLR, PLR, and CRP level [19].

In another study that assessed the relationship between SII, NLR, and PLR and Major adverse cardiac events (MACE) that occurred in a hospital setting and at 50 months of follow-up. MACE was defined as re-infarction, and target vessel revascularization. Of the 1103 individuals, ST-elevation myocardial infarction affected 403 of them, whereas non-ST-elevation myocardial infarction affected 700. One group of patients had MACE, and the other did not [20].

In 195 patients (17.7%), MACE was noted in both in the hospital and throughout the 50-month follow-up. The result of this study found that age, WBC, CRP and SII were found to be co-independent predictors of MACE in both the whole population and in patients with STEMI and NSTEMI. The SII level showed superior diagnostic performance than WBC, CRP, NLR and PLR in predicting MACE in the whole population. MACE risk was 48.7 times higher in those with SII level > 955.8 compared to those with a level 955.8 [21].

The predictive value of SII level in predicting MACE in STEMI patients were found to be > 916.7, with 82.9% sensitivity and 83.2% specificity, and MACE risk was found to be 24.6 times higher in patients with SII level > 916.7 compared to those with a level ≤ 916.7 (HR: 24.6; 95% CI = 14.4–42.1; p < 0.001). on the other hand, the predictive value of SII level in predicting MACE in NSTEMI patients was found to be > 986 with 78.2% sensitivity and 90.7% specificity, and MACE risk was found to be 97.1 times higher in those with SII level > 986 compared to those with a level ≤ 986 (HR: 97.1; 95% CI = 59.2–159.1; p < 0.001) [21].

Table 3: Conventional Vs. Novel Emerging Biomarkers

Biomarker	Details	Outcome(s)	Follow-Up	n	Predictor/Cut-Off Value	Reference
SII NLR PLR	AMI+ coronary angiography	MACE	50-month	1103	STEMI SII> 916.7 NSTEMI SII > 986	[21]
SII	CAD	Severity and occurrence of CAD	N/A	395	Higher	[19]
NLR					Lower	
PLR					Lower	
CRP					Lower	
SII	STEMI who underwent pPCI	Intracoronary thrombus burden	N/A	425	Higher	[17]
NLR					Lower	
PLR					Lower	
SII	Short-term outcomes after Off-pump CABG	MACEs, duration of MV <24 hours, new-onset RF, sepsis & death	N/A	1007	Higher	[18]
NLR					Lower	
PLR					Lower	
SII	STEMI	MACE: CV death, MI, or stroke Cardiac death Non-fatal MI HHF Revascularization (PCI or CABG)	34.2 months	843	≥554.9	[16]
NLR						
PLR						

SII	CAD	MACCEs	5-year	157	>615	[20]
CRP						
Platelets						
PLR						

Abbreviations: SII, systemic inflammatory index; NLR, normocyte-to-lymphocyte, PLR, platelet-to-lymphocyte ratio; CAD, coronary artery disease; AMI, acute myocardial infarction; MACE, major adverse cardiac event; CV, cardiovascular; pPCI, primary percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; STEMI, ST elevation myocardial infarction; HHF, hypertensive heart failure; CABG, coronary artery bypass graft; MACCEs, major adverse cardiovascular and cerebrovascular events.

Conclusion

The goal of our review was to develop an up-to-date picture of the prognostic usefulness of both established and newly discovered biomarkers in predicting the complications that is ischemia-related cardiovascular diseases. The conventional biomarkers were effective in determining and predicting the CVD-related complications, yet none of them was able to stand alone or significantly predict the poor outcomes [6-9].

The SII, SIRI and even the very recently novel biomarker, SIIRI, are showing a promising result of being the independent predictor for the complications and severity of cardiovascular diseases which will be reflected positively and significantly on the treatment and plan of care for CVD patients by avoiding and lessening a potential short and long-term complications [10-15].The novel emerging biomarkers were developed to be more specific and reliable that could independently be a predictor of complications that is associated with the CVDs. The biomarker SII and was tested thoroughly and showed satisfactory results up to this moment as an independent predictor of outcomes, in comparing to the conventional biomarkers, taking into account that novel emerging biomarker is simple, cheap, routinely performed in the hospitals as it is CBC-type of tests, and easy to be obtained, followed up and calculated [17,18,21]. It appears that despite substantial research, a unique, ideal biomarker that has high sensitivity and specificity, is bias-free, affordable, simple to determine, and widely accessible is still out of reach at this time. Although many humoral parameters have been tested, a definite conclusion cannot be drawn on any of them. Additionally, there were significant differences between studies in terms of the patient enrollment rates, outcomes monitored, and study methods. The use of various laboratory kits for the same parameter in some situations may have led to results that were heterogeneous. The developing biomarkers do not currently have set standard cut-off values. Further study is required, and focus should be placed on standardization and focused applicability in order to develop a really valuable humoral prognostic measure. This objective is still out of reach.

Conflict of Interest

All authors declare the No conflict of interest.

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Declaration of using Artificial Intelligence

The authors use AI for paraphrasing certain paragraphs to enhance clarity of the English language.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Author Contribution

The search was performed by all authors. The articles appraisals were completed by all authors. The research summary following the PRISMA was performed by all authors. The Methodology and results were written by Salameh, A. The introduction was made by the first two authors. The conclusion was completed by the last two authors. The manuscript was reviewed and revised by Salameh, A., & Al-Hmaimat, A. Finally, all authors have read and agreed to the published version of the manuscript.

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