Journal of Advances in Medicine and Medical Research

Volume 35, Issue 19, Page 219-229, 2023; Article no.JAMMR.103449
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Calprotectin as Biomarker in Cardiovascular Disease: A Systematic Review

Maryam Iqbal [a], Chisom Euphemia Alakwe-Ojimba [b], Eunice Kosisochukwu Omeludike [c], Akata Abung [d], Kholood Ahmed [e], Oluwatobiloba Frances Fasoranti-Sowemimo [f*], Madiha Haseeb [g], Oluwaseun Christiannah Sadare [h], Osamwonyi Osagie Abel [i], Janet A. Omole [j], Mendha Akash Ajaykumar [k], Aamna Shanzay Iftikhar [l], Rakesh Kumar Das [m], Okika Ebuka Jude [n] and Sobner Aubourg [h]

[a] CMH Lahore Medical College and Institute of Dentistry, Pakistan.
[b] Chukwuemeka Odumegwu Ojukwu University College of Medicine, Nigeria.
[c] College of Health Sciences, University of Port Harcourt, Nigeria.
[d] College of Medicine, University of Calabar, Nigeria.
[e] Howard University, USA.
[f] Obafemi Awolowo University College of Health Sciences, Ile-Ife, Nigeria.
[g] Dow University of Health Sciences (SMC), Pakistan.
[h] Windsor University School of Medicine, Saint Kitts and Nevis.
[i] Caribbean Medical University, Curacao.
[j] Advocate Christ Medical Center, USA.
[k] Grodno State Medical University, Belarus.
[l] Shalamar Medical and Dental College, Pakistan.
[m] New York City Health and Hospitals/Lincoln Medical Center, NY, USA.
[n] V.N Karazin Kharkiv National University, Ukraine.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i195154

**Corresponding author: E-mail: sowemimotobiloba@gmail.com;*

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/103449

Systematic Review Article

Received: 17/05/2023
Accepted: 24/07/2023
Published: 02/08/2023

ABSTRACT

Background: Calprotectin, also known as S1008/A9 or MRP8/14, is a peptide secreted during active immune responses that serves as an indicator of inflammation. It has been widely studied as a biomarker for various inflammatory diseases, including inflammatory bowel diseases. Recent research has explored the potential prognostic and diagnostic implications of calprotectin in cardiovascular and cardiometabolic diseases, which are associated with chronic inflammation. Elevated levels of calprotectin have been positively associated with the severity and adverse outcomes of cardiovascular diseases, such as stroke, myocardial infarction, and heart attack. The underlying mechanisms through which calprotectin contributes to the pathology of cardiovascular disease are not fully understood but may involve promoting inflammation, oxidative stress, endothelial dysfunction, and plaque destabilization within blood vessels. This review summarizes the current knowledge regarding the role of calprotectin as a biomarker for prognostic and diagnostic abilities in predicting the progression and severity of cardiovascular diseases.

Methods: This systematic review followed the PRISMA guidelines and identified relevant studies through a comprehensive search of electronic databases.

Results: Several studies have demonstrated an association between calprotectin levels and cardiovascular risk, including studies on patients with peripheral arterial disease, acute coronary syndrome, Kawasaki disease, and systemic lupus erythematosus. These findings suggest that calprotectin could serve as a useful prognostic factor, providing additional insights into the underlying inflammatory processes and aiding risk stratification and treatment decisions.

Conclusion: Further research is needed to validate its clinical utility and establish standardized measurement protocols for calprotectin in the context of cardiovascular and cardiometabolic diseases.

Keywords: Calprotectin; cardiovascular; biomarker; screening; diagnosis.

1. INTRODUCTION

Calprotectin, also known as S1008/A9 or MRP8/14, is a peptide secreted during an active immune response and serves as an indicator of inflammation [1]. It plays a role in various inflammatory processes, and is actively secreted by neutrophils and monocytes. During inflammation, it can be found in extracellular fluids. Its presence in fecal samples makes it an excellent biomarker to monitor inflammatory bowel diseases such as Crohn's disease and Stomach ulcers [2]. Many recent studies have tested calprotectin as a potential prognostic and diagnostic biomarker for other inflammatory diseases. Some studies suggest that calprotectin could also be useful prognostic implications for cardiovascular and cardiometabolic diseases, which are associated with chronic inflammation [3]. The mechanism through which calprotectin is contributing to the pathology of cardiovascular disease is still not fully clear. However, it is believed that calprotectin promotes inflammation, oxidative stress, endothelial dysfunction, and plaque destabilization within the blood vessels, all of which are crucial processes in the development of cardiovascular diseases [4]. Overall, the emerging evidence suggests that calprotectin could serve as a useful prognostic factor for cardiovascular and cardiometabolic diseases, providing additional insights into the underlying inflammatory processes and

potentially aiding in risk stratification and treatment decisions [1]. However, further research is necessary to validate its clinical utility and establish standardized measurement protocols for calprotectin in these contexts.

Chronic inflammation is a contributing factor in the development and progression of conditions like atherosclerosis, coronary artery disease, and acute coronary syndromes [5]. Elevated levels of calprotectin have been positively associated with the severity of cardiovascular disease. Adverse outcomes of cardiovascular disease have been linked with elevated levels of calprotectin in stroke, myocardial infarction, and heart attack [6]. It has been proposed that calprotectin can not only act as a biomarker of cardiovascular diseases but can also identify individuals with a higher risk of developing cardiovascular disorders and predict the course of the atherosclerotic process. Cardiovascular disease (CVD) is diagnosed using various biomarkers, including hsCRP, troponin, lipid profile, and natriuretic peptides. However, these biomarkers have limitations such as non-specificity, lack of accuracy, and influence by other factors [7]. The need for new biomarkers arises to provide improved risk prediction, early detection, specificity, precision, mechanistic insights, and monitoring of treatment response. The development of new biomarkers can lead to better management and prevention of CVD, and ongoing research efforts are working toward identifying and validating such biomarkers.

The current systematic review aims at summarizing current knowledge and studies discussing the role of calprotectin as a possible biomarker for the prognostic and diagnostic abilities of calprotectin to predict the progression and severity of cardiovascular diseases. The development of new biomarkers, such as calprotectin, has the potential to improve risk prediction, early detection, specificity, precision, mechanistic insights, and monitoring of treatment response in cardiovascular diseases, leading to better management and prevention strategies.

2. METHODS

The systematic review conducted in this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 guidelines, ensuring a rigorous and transparent approach. The study selection process followed the PICO framework, which stands for Population, Intervention, Comparator, and Outcomes. This framework helped in defining the criteria for including relevant articles. To identify suitable studies, a comprehensive search was performed in electronic databases, including PubMed and Google Scholar. The search encompassed articles published from January 2012 until May 15, 2023. The inclusion criteria comprised randomized controlled trials, observational studies, and cohort studies involving patients with cardiovascular diseases. The focus was on evaluating the role of calprotectin as a possible biomarker for CVD. The search terms employed various keywords related to Calprotectin, S1008/A9, or MRP8/14. Boolean logic (using "and/or") was applied to refine the search. Only studies published in English were considered, while case reports, case series, and reviews were excluded. Data synthesis and reporting were performed using a combination of tabular and textual formats. A standardized data extraction form was utilized to extract key information from the included studies. This form included details such as author names, publication year, study design, sample size, characteristics of the population, outcome measures assessed, study results, limitations, and conclusions. This structured approach allowed for systematic data extraction and comparison across studies. Additionally, a referencing management tool called Mendeley was used throughout the systematic review process to effectively manage citations and full-text articles. The PRISMA flowchart for included studies is given in Fig. 1.

3. RESULTS

In the process of database searching, a comprehensive set of 288 studies was initially identified. Following the elimination of 40 duplicate entries, 248 studies underwent screening based on their titles and abstracts. As a result, 188 records were excluded as they did not meet the predetermined inclusion criteria. The remaining 60 articles were evaluated in their entirety to determine eligibility. Out of these, 48 articles were subsequently excluded as they did not meet the inclusion criteria. A total of 12 studies were deemed suitable for inclusion in the systematic review, as illustrated in Fig. 1. The characteristics of included studies are listed in Table 1.

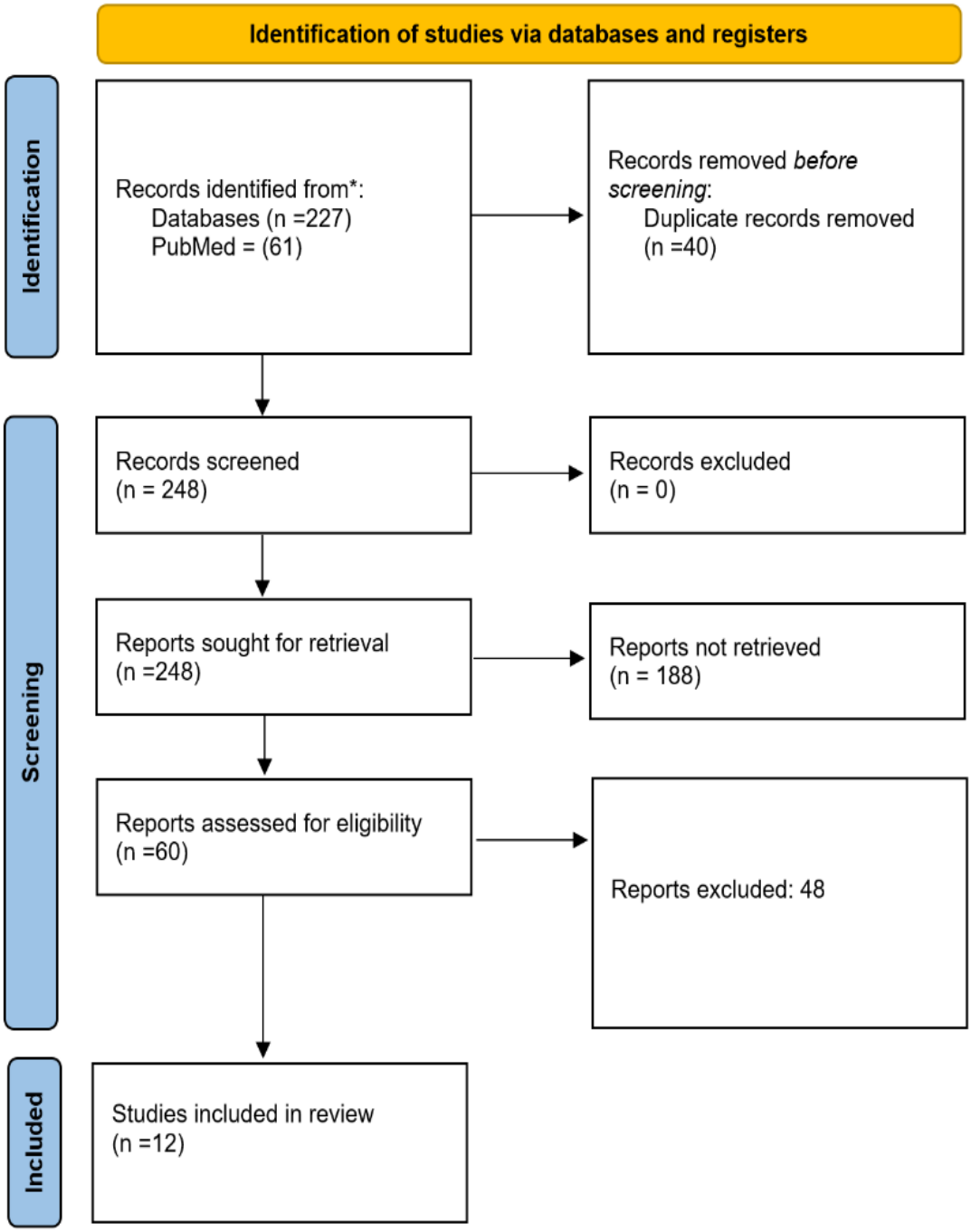

Fig. 1. PRISMA flowchart depicting the study selection process

The majority of the patient cohorts comprises predominantly male patients partly due to the high incidence of CVD in males as compared to females. The total sample size comprises 16,028 patients suffering from various heart conditions including 26 children suffering from Kawasaki disease. The studies recruited 445 controls and the population was predominantly male individuals. The studies included were mostly conducted on small patient cohorts, with only two studies that recruited more than 5000 patients and monitored the patients in follow-up visits for more than 5 years [8,12].

Kunstor et al 2018, conducted an observational study that aimed to investigate the relationship between calprotectin and the risk of cardiovascular disease (CVD). The study

involved measuring calprotectin levels in the blood of 5290 participants and following them over 8.3 years to record any CVD events. The results showed that higher levels of calprotectin were associated with an increased risk of CVD, even after adjusting for other established risk factors such as high-sensitivity C-reactive protein (hs-CRP), triglycerides, and body mass index. The association between calprotectin and CVD risk was consistent across different subgroups of participants and adding calprotectin to conventional risk factors improved the accuracy of CVD risk assessment [8].

Another study by Saenz-Pipaon et al. (2022) discussed the use of two biomarkers, Lipocalin-2 (LCN2) and calprotectin, for predicting cardiovascular risk in patients with peripheral arterial disease (PAD). The biomarkers were examined in human femoral plaques and the blood of PAD patients. The study found that high levels of LCN2 and calprotectin were associated with an increased risk of cardiovascular death or amputation in both advanced and early PAD patients. The addition of these biomarkers to existing risk assessment models improved risk stratification.

Wang et al., 2020 investigated the relationship between S100A8/A9 and the occurrence of very late stent thrombosis (VLST) in patients with acute myocardial infarction (AMI). It is pertinent to note that all three proteins (S100A8, S100A9, and S100A12) are structurally and functionally related and have been implicated in inflammatory processes. Calprotectin is a heterodimeric complex formed by S100A8 and S100A9, and it is often used as a surrogate marker for the measurement of these proteins. Calprotectin is released by activated neutrophils and monocytes during inflammation, and its levels can be measured in blood, as well as in stool, as a marker of gastrointestinal inflammation. VLST is a serious complication that can happen months to years after coronary stent implantation, leading to adverse cardiovascular events. The study included 8,476 patients with AMI who had previously undergone coronary stent implantation. Blood samples were collected, and the levels of S100A8/A9 were measured. The patients were then followed up for a median duration of 38 months to determine the occurrence of VLST. The results showed that patients who developed VLST had significantly higher levels of S100A8/A9 compared to those who did not experience VLST. Additionally, the levels of S100A8/A9 were positively correlated with the occurrence of VLST, even after adjusting for other risk factors such as age, sex, and medication use. Based on these findings, the authors concluded that elevated levels of S100A8/A9 are associated with an increased risk of developing VLST in patients with AMI. The study suggests that S100A8/A9 may serve as a potential biomarker for identifying patients at higher risk of VLST and may have implications for risk stratification and personalized treatment approaches in this population.

Mjelva et al. (2013) evaluated the usefulness of two biomarkers, Pregnancy-Associated Plasma Protein A (PAPP-A) and calprotectin, in predicting adverse outcomes in patients with suspected acute coronary syndrome (ACS). ACS is a condition in which the blood supply to the heart is suddenly blocked, leading to a heart attack. The study included 871 patients with suspected ACS who were followed up for an average of 84 months. The results showed that high levels of pregnancy associated plasma protein-A (PAPP-A) and calprotectin were associated with increased mortality and other adverse outcomes in these patients. However, neither biomarker was found to be an independent predictor of long-term prognosis. Overall, the study suggests that PAPP-A and calprotectin may be useful in identifying patients at higher risk of adverse outcomes in the short term, but further research is needed to determine their long-term prognostic value [10].

Fabi et al. (2022) worked on Kawasaki Disease (KD), which is a type of vasculitis that affects medium-sized vessels in children. The purpose of the study was to determine if fecal calprotectin (FC) can be used to predict the development or persistence of coronary artery lesions (CALs) in children with KD. The study involved collecting data on clinical symptoms, laboratory results, echocardiograms, and FC levels during the acute and subacute phases of KD. The results showed that a combination of FC levels higher than 250 microgram/g and a z-score higher than 2 during the acute phase of KD was associated with the persistence of CALs. Additionally, high levels of neutrophils and white blood cells during the acute phase, as well as high levels of C-reactive protein (CRP) at KD onset, were also associated with the presence of CALs during both the acute and subacute phases. Therefore, the study suggests that in children with low initial CRP levels, the combined assessment of FC and z-score levels during the acute phase of KD can serve as a reliable predictor for the persistence of CALs.

Table 1. Basic characteristics and outcomes of the selected studies

	Author, Year	Methodology	Cardiovascular disorder	Participants	Outcomes
1	Kunutsor et al. (2018) [8]	PREVEND prospective study for 8.3 years	IHD, AMI CABG, PTCA, IHD, fatal or nonfatal MI, CABG.	N=5290 (Without CVD=4951, CVD= 339), Male =2530	There is a log-linear association of calprotectin concentration with the risk of CVD, which may be partly dependent on hsCRP; adding calprotectin to conventional risk factors improves CVD risk assessment using measures of reclassification and −2 log-likelihood
2	Saenz-Pipaon et al. (2022) [9]	Population-based screening for 4 years	PAD	744 (CVD cohort n=331, VIVA PAD cohort n= 413), Male =714	LCN2 and S100A9 were detected in human plaques in regions rich in inflammatory cells
3	Mjelva et al. (2013) [10]	Prospective, observational study	ACS	N= 871, Male=482	High levels of PAPP-A and calprotectin were associated with adverse clinical outcomes in chest pain patients with clinically suspected ACS
4	Yu et al. (2022) [11]	Case-control/ prospective study	NSTEMI, STEMI	80 control individuals, 63 NSTEMI and 59 STEMI patients	Plasma levels of MPO-DNA and S100A8/A9 in the STEMI and NSTEMI groups were significantly higher than in the control group
5	Wang et al. (2020) [12]	Observational study	VLST in MI	56 patients/ group (cohort of 8476) and 112 controls	During VLST, there was a significant increase in S100A8/A9 levels compared to its levels during index PCI; this increase was different from the changes observed in hs-CRP levels; higher serum levels of S100A8/A9 are linked to the development of VLS
6	Fabi et al. (2022) [13]	Prospective monocentric study	Kawasaki Disease	26 children	FC > 250 microgram/g and a z-score > 2 during the acute phase of KD can predict CALs persistence, particularly in children with initial CRP < 13 mg/dl
7	Buyukterzi et al. (2017) [14]	Case-control prospective	ACS	90 participants (30 patients with normal coronary arteries; 30 patients with stable coronary artery disease; and 30 patients with acute coronary syndrome)	S100A9 levels were higher in ACS than in normal coronary artery groups (p = 0.033); S100A12 levels were higher in ACS than in patient groups with normal coronary arteries and patient groups stable coronary artery disease (p = 0.001)
8	Tydén et al. (2013) [15]	Case-control	SLE	237 SLE patients, 100 healthy individuals.	Serum levels of S100A8/A9 were higher in inactive SLE patients compared to healthy

				Male= 31	individuals (P < 0.0001), but there was no significant difference in S100A12 levels (P = 0.12); SLE patients with a history of CVD had higher levels of both S100A8/A9 and S100A12 compared to those without CVD or venous thromboembolism (P = 0.003 and P = 0.006, respectively)
9	Cotoi et al. (2014) [16]	Observational study	CVD	664 individuals aged 63 to 68 years, with no previous history of CV disease, were randomly selected. Male= 266.	High levels of plasma S100A8/A9 are influenced by factors such as smoking, high body mass index, high glycosylated hemoglobin A1c, and low-density lipoprotein; high-density lipoprotein has a negative association with S100A8/A9; Both S100A8/A9 and circulating neutrophils are positively correlated with intima-media area in the common carotid artery and have similar associations with the incidence of coronary events and cardiovascular death
10	Jonasson et al. (2017) [17]	Observational case-control	CAD	60 CAD patients, psychological stress, a cohort of 27 CAD patients and 28 controls Male= 96	Acute psychological stress induces elevated levels of S100A8/A9
11	Jensen et al. (2012) [18]	Case-control	CHF	193 CHF patients, 100 healthy controls Male = 182	The levels of plasma calprotectin were significantly increased in the CHF patients compared to the control group (P < 0.01); plasma calprotectin was a superior biomarker of high NYHA classes than other parameters reflecting CHF severity, OR 2.2 (1.1–4.3) (P = 0.019)
12	Fang et al. (2014) [19]	Observational study	ACS	UAP group, n=51, AMI group, n=50, SAP group, n=25, NC group, n=25. Male= ?	The S100A8/A9 level in the SAP group was significantly higher than that in the normal control group (P<0.05); serum levels of S100A8/A9 in the UAP group and the AMI group were significantly higher than that in the SAP group

ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; CABG: Coronary Artery Bypass Grafting; CHF: Chronic Heart Failure; IHD: Ischemic Heart Disease, AMI: Acute Myocardial Infarction; LCN2: Lipocalin 2; MPO-DNA: Myeloperoxidase Deoxyribonucleic Acid; NSTEMI: non-ST-Segment Elevation Myocardial Infarction; NYHA: New York Heart Association; PAPP-A: Pregnancy Associated Plasma Protein-A; PAD: Peripheral Arterial Disease; PREVEND: Prevention of Renal and Vascular end-Stage Disease; PTCA: Percutaneous Transluminal Coronary Angioplasty; SAP: Stable Angina Pectoris; STEMI: ST-segment Elevation Myocardial Infarction; UAP: Unstable Angina Pectoris; VIVA: Vascular Interventional Advances; VLST: Very Late Stent Thrombosis

Buyukterzi et al. (2017) studied whether the levels S100A8, S100A9, and S100A12 (i.e., these proteins that belong to the S100 protein family; they are known as calcium-binding proteins and are involved in various cellular processes, including inflammation and immune response) in the blood could be used as markers for acute coronary syndrome (ACS). Patients who underwent certain heart procedures were recruited and divided into three groups based on their diagnosis (normal coronary arteries, stable coronary artery disease, and ACS). Blood samples were taken and the levels of the proteins and other markers were measured. The results showed that levels of S100A9 were higher in ACS patients compared to those with normal coronary arteries, and levels of S100A12 were higher in ACS patients compared to both normal coronary arteries and stable coronary artery disease. S100A12 was also identified as an independent associate of ACS. The study suggests that S100A12 could be used as a marker for coronary plaque instability and may have implications for ACS treatment.

Tydén et al., 2013 investigated the association between CVD and two S100A8/A9 and S100A12 in patients with systemic lupus erythematosus (SLE). SLE patients have an increased risk of CVD, which is believed to be partly due to the persistent inflammation seen in SLE. The study measured the levels of S100A8/A9 and S100A12 in the serum of 237 SLE patients with clinically inactive disease and without infections, as well as in 100 healthy individuals. The presence of CVD and organ damage was also assessed. The results showed that SLE patients with a history of CVD had higher levels of both S100A8/A9 and S100A12 compared to those without CVD. Additionally, the presence of organ damage was associated with increased levels of both proteins. The study suggests that elevated levels of these proteins may be indicative of severe disease and CVD in SLE patients and may warrant more intense cardiovascular prevention strategies and early immunosuppressive treatment.

Cotoi et al., 2014 investigated the correlation between S100A8, A9, and A8/A9 and carotid artery disease and cardiovascular (CV) risk in apparently healthy individuals. The study found that plasma S100A8/A9 concentration is positively influenced by circulating neutrophil numbers, smoking, body mass index, glycosylated hemoglobin A1c, and low-density lipoprotein, and negatively influenced by high-density lipoprotein. S100A8/A9 and circulating neutrophils were found to be positively correlated with the intima-media area in the common carotid artery, independently of age, sex, and CV risk factors. S100A8/A9 and circulating neutrophils also presented similar associations with the incidence of coronary events and CV death, particularly in women. However, there were no independent relationships between S100A8 and S100A9 and CV disease. The study suggests that S100A8/A9 may be a potentially important link between neutrophils, traditional CV risk factors, and CV disease [16].

Jonasson et al. (2017) investigated the release of S100A8/A9 and parameters of anti-inflammatory glucocorticoid secretion in patients with coronary artery disease (CAD). The study aimed to explore the pathways and mediators involved in cardiovascular events triggered by psychological stress. In the first cohort of 60 CAD patients subjected to a psychological stress test, it was found that psychological stress caused a rapid increase in circulating levels of S100A8/A9. This quick response of S100A8/A9 strongly correlated with elevated levels of evening saliva cortisol, indicating a potential association with a dysregulated hypothalamic-pituitary-adrenal (HPA) axis, which is involved in stress response. In the second cohort consisting of 27 CAD patients and 28 controls, it was observed that elevated levels of S100A8/A9 were still present 24 hours after stress in 40% of patients and 36% of controls. There was a tendency for higher levels of S100A8/A9 in patients compared to controls. The sustained release of S100A8/A9 was associated with a poor rapid cortisol release after stress, but only in the patient group and not in the control group. This suggests that CAD patients may have a dysregulated cortisol secretion in response to stress, which could contribute to an exaggerated pro-inflammatory response of S100A8/A9.

Jensen et al. (2012) investigated whether calprotectin could be a useful biomarker for chronic heart failure (CHF). The study found that plasma calprotectin levels were significantly higher in CHF patients compared to healthy controls, especially in those with more severe CHF (New York Heart Association class III and IV). Calprotectin was found to be a better indicator of CHF severity than other parameters. However, plasma calprotectin levels did not predict mortality in CHF patients. The study suggests that inflammatory activity is upregulated in CHF and may be associated with the severity of the condition.

Fang et al. (2014) reported higher serum levels of the S100A8/A9 protein complex in patients with acute coronary syndrome (ACS) and its relation to the severity of coronary lesions. The study involved 126 patients with coronary heart disease, including unstable angina pectoris (UAP), acute myocardial infarction (AMI), and stable angina pectoris (SAP), as well as a control group of healthy volunteers. The serum levels of S100A8/A9 were measured using an enzyme-linked immunosorbent assay and compared among the various groups. The study found that the serum level of S100A8/A9 was significantly elevated in patients with ACS and correlated positively with the number of coronary lesion branches. However, there was no correlation between the serum level of S100A8/A9 and short-term prognosis in patients with ACS. S100A8/A9 is a calcium-binding protein complex that is involved in various inflammatory processes and has been implicated in cardiovascular diseases.

4. DISCUSSION

Cardiovascular diseases (CVDs) are a major health concern worldwide and are caused by lifestyle and genetics. CVDs involve many physiological processes, and physical signs and medical history are used to predict their development, but often the disease is only detected at a late stage. Biomarkers have been identified to detect CVD early, allowing for earlier treatment and improving quality of life. The first cardiac biomarker was discovered in 1954, and since then, several biomarkers have been recognized for assessing various stages of CVDs [20]. Commonly used biomarkers include natriuretic peptides, blood glucose, cholesterol levels, C-reactive protein, and homocysteine. However, many biomarkers are affected by non-cardiac factors, and efforts are being made to identify more specific and effective biomarkers. Metabolites can also be used as biomarkers for CVDs, with nitric oxide being one example [21]. Overall, biomarkers offer an important tool for early detection, targeted therapy, and prognostic insights for CVDs.

An ideal biomarker in CVD should be able to identify patients with chest pain of an ischemic etiology (angina) and differentiate between acute myocardial infarction (MI) and unstable angina, acute pulmonary embolism, or aortic dissection. In addition, it should also assess the therapeutic response, the extent of myocardial damage, severity of underlying coronary disease, degree of left ventricular dysfunction, risk of future recurrences, and progression to heart failure in patients with established acute MI. In addition, for a biomarker to be clinically valuable, it must be accurate, reproducible, acceptable to the patient, easy to interpret, and have high sensitivity and specificity for the outcome it is expected to identify [22]. Although the review identified studies supporting calprotectin as a possible biomarker for identifying the risk of CVD along with measuring the severity of the condition, however, no study was designed to establish the causation of CVD with calprotectin.

The identification of new cardiac biomarkers in predicting the risk of developing cardiovascular diseases (CVDs) and guiding lifestyle modifications and medications for high-risk patients is very important for prevention and treatment regimens [23]. Multiple biomarkers need to be tested to improve accuracy, and certain combinations of biomarkers have shown high predictive performance. The use of biomarkers is also important in managing symptoms and identifying the risk of developing CVD complications in individuals with chronic diseases. However, there are limitations to using biomarkers, such as their sensitivity and specificity, variability due to medication and nutritional status, and uncertainty about whether they are the cause or consequence of a disease. Further research is needed to validate newly identified biomarkers like exosomes, miRNAs, and nucleotides. Overall, evaluating cardiac biomarkers in larger patient cohorts can help identify a gold standard biomarker for CVD risk assessment.

The systematic review identified a total of 12 studies that investigated the association between various biomarkers, such as calprotectin, S100A8/A9, Lipocalin-2 (LCN2), and Pregnancy-Associated Plasma Protein A (PAPP-A), and cardiovascular disease (CVD) or related conditions. These studies shed light on the potential role of these biomarkers in predicting cardiovascular risk, assessing disease severity, and identifying patients at higher risk of adverse outcomes. This study focused on calprotectin and its relationship with the risk of CVD. The findings indicated that higher levels of calprotectin were associated with an increased risk of CVD, even after adjusting for established risk factors. This suggests that calprotectin could serve as a valuable biomarker for CVD risk assessment, enhancing the accuracy of current risk prediction models. However, it is important to

note that these studies have limitations, including small sample sizes, lack of data on certain variables, inability to establish causality, and limited generalizability of results. Further research with larger populations and longer follow-up periods is needed to determine the long-term prognostic value of these biomarkers and establish their utility in risk prediction and personalized treatment approaches.

4. CONCLUSION

In conclusion, this systematic review of studies examined the association between various calprotectin and cardiovascular disease (CVD) which revealed valuable insights into its potential as predictors of cardiovascular risk, disease severity, and adverse outcomes. The included studies focused on biomarkers such as calprotectin, S100A8/A9, Lipocalin-2 (LCN2), Pregnancy-Associated Plasma Protein A (PAPP-A), and others. Overall, the reviewed studies highlight the potential utility of calprotectin in assessing cardiovascular risk, disease severity, and adverse outcomes. However, further research is necessary to validate their clinical applicability, establish optimal cutoff values, and determine their independent prognostic value. Nonetheless, these findings contribute to the growing body of evidence supporting the use of biomarkers in cardiovascular risk assessment and personalized treatment approaches.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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