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The S100A8/A9 Axis in Acute Myocardial Infarction: Connecting Innate Inflammation to Myocardial Damage and Clinical Risk

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Abstract: Acute myocardial infarction (AMI) is a predominant cause of morbidity and mortality globally, with post-infarction heart failure serving as a significant factor in long-term prognosis. In addition to myocardial ischemia and necrosis, the early onset of sterile inflammation significantly affects infarct expansion, ventricular remodeling, and ensuing cardiac dysfunction. The identification of biomarkers that indicate these upstream inflammatory pathways is still an unresolved clinical necessity. AMI initiates a swift innate immune response marked by neutrophil activation and the release of the S100A8/A9 heterodimer comprising the calcium-binding proteins S100A8 and S100A9, which has surfaced as a pivotal pro-inflammatory mediator in cardiovascular disease. Subsequent to cardiac ischemia, S100A8/A9 is facilitating ischemia-reperfusion damage via innate immune signaling pathways. S100A8/A9, besides its role in acute myocardial injury, modulates leukocyte recruitment, cytokine synthesis, and fibroblast activation, therefore influencing post-infarction scar formation and ventricular remodeling. Recent clinical findings suggest that circulating S100A8/A9 provides predictive information that exceeds conventional biomarkers by reflecting the intensity of inflammation-driven pathological processes. S100A8/A9 levels increase promptly during acute myocardial infarction (AMI), frequently occurring before BNP elevation and supplementing troponin I by elucidating inflammation-mediated mechanisms that contribute to ventricular remodeling and the risk of heart failure, rather than solely indicating myocardial injury or wall stress. These characteristics facilitate its developing function as a prognostic biomarker and a prospective therapeutic target in the treatment of patients post-AMI.

Keywords: S100A8/A9, Biomarker, Cardiovascular Diseases, Acute Myocardial Infarction, Calprotectin, Neutrophils, Inflammation, Ischemia/Reperfusion Therapeutic Target.

Review Paper

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1. INTRODUCTION

Acute myocardial infarction (AMI) continues to be the primary source of disease burden worldwide [1, 2]. Acute myocardial infarction (AMI) begins with the partial or complete occlusion of the coronary arteries, which reduces blood flow to the cardiac muscle; this reduction eventually leads to tissue ischemia, and if the ischemia persists, necrosis (infarction) of the heart muscle occurs. Acute myocardial infarction (AMI) remains a globally challenging health issue despite the advances in treatment modalities [3].

Atherosclerosis is the principal underlying cause of most acute coronary syndromes, with approximately 90% of myocardial infarctions (MIs) resulting from acute thrombotic occlusion of atherosclerotic coronary arteries [4]. The process typically begins with the rupture or erosion of an unstable atherosclerotic plaque, which triggers platelet activation and thrombus formation. This procedure subsequently leads to obstruction of coronary blood flow, resulting in myocardial ischemia, cardiomyocyte injury, necrosis, and eventual ventricular remodeling [5].

Both the initial tissue injury and the subsequent healing phases are influenced by the inflammatory response (mainly led by activated leukocytes and pro-inflammatory cytokines) unleashed by tissue necrosis that, though partially beneficial to remove debris and promote healing, may prove to be deleterious if uncontrolled [6].

Early revascularization therapies, such as percutaneous coronary intervention (PCI) and

thrombolysis, have improved the survival rate, but post-AMI complications continue to be prevalent [7]. These include arrhythmia, mechanical dysfunction (e.g., heart failure), thrombosis, and inflammatory complications (e.g., pericarditis) [8].

The diagnosis of AMI requires the use of traditional biomarkers, such as cardiac troponins and creatine kinase-MB (CK-MB); however, these offer little information about the long-term prognosis. Therefore, there is growing interest in identifying novel biomarkers that can better reflect myocardial inflammation, oxidative stress, and tissue remodeling [9-10]. Among these, the S100 protein family has been implicated in the occurrence and development of multiple cardiovascular diseases, and these proteins are expected to become new targets for prevention. [11] Particularly the S100A8/A9 heterodimer—has emerged as a potential indicator of inflammation-associated myocardial injury, offering new perspectives for early detection and targeted therapy [12].

Here, we elaborate on the critical roles and potential mechanisms of S100A8/A9 in driving the pathogenesis of AMI. First, the structural properties of the S100A8/S100A9 complex are discussed. Then we highlight the expression and distribution of the S100A8/A9 heterodimer. Moreover, the predictive value of S100A8/A9 for the risk of recurrence of cardiovascular events is elucidated. Therefore, this review focuses on the molecular mechanisms of S100A8/A9 in MI pathogenesis to provide a promising biomarker and therapeutic target for AMI.

2- Structural Properties of the S100A8/S100A9 Complex

Human calprotectin (CLP, S100A8/S100A9 oligomer, MRP8/MRP14 oligomer) is a Ca^{2+}-binding 93/114-amino acid protein with respective molecular weights of 10.8/13.2 kDa [13]. CLP, belonging to the S-100 protein family, which is the most stable form in vivo, is a heterodimer (and sometimes heterotetrameric) protein complex composed of two small, human, calcium-binding proteins, S100A8 and S100A9 [14]. CLP, characterized by its ability to bind both calcium and transition metals [15].

S100A8 and S100A9 are important members of the S100 family and are also named myeloid-related protein 8 (MRP8) and MRP14, respectively. They share a high degree of structural similarity, despite having only 25%–65% similarity in amino acid sequences [5]. Figure (1)

The two proteins are not detected as monomers but form various noncovalent homo- or hetero-oligomers related to specific activities in human physiology. 16 They primarily form heterodimers known as calprotectin, although heterotetramers can form under high calcium concentrations, providing greater structural stability.

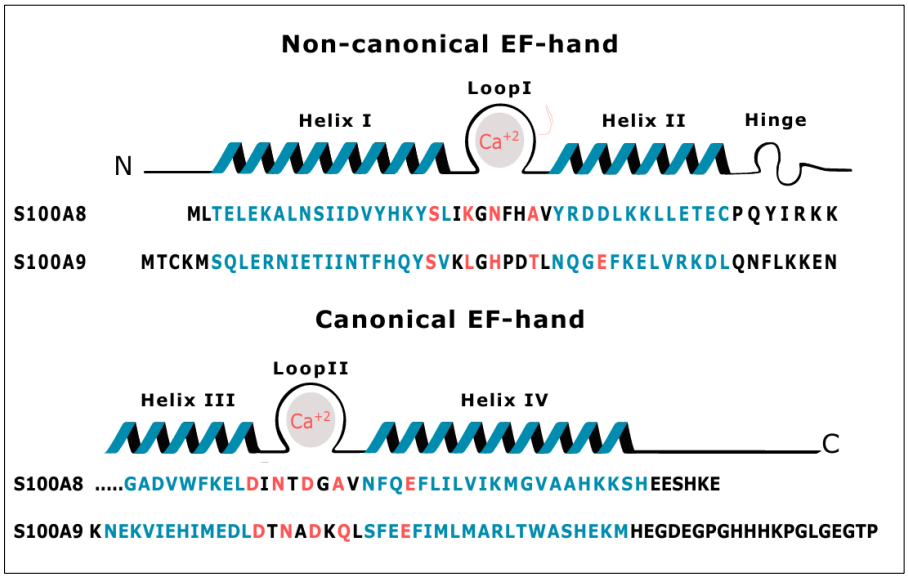

Figure 1: Structure-based amino acid sequence alignment of human S100A8 and S100A9. The structural elements are schematically highlighted above the alignment, including helices (helix 1 and helix Ⅰ Ⅰ in the N-terminal EF-hand motif; helix Ⅲ and helix Ⅳ in the C-terminal EF-hand motif), Ca^{2+}-binding loop Ⅰ and loop Ⅰ Ⅰ (the transition-metal binding residues are shown in magenta), and the hinge region. Structural data and sequences retrieved from RCSB PDB (ID: 1XK4)

The calprotectin molecular structure consists of an EF-hand-type Ca^{2+}-binding domain. Each subunit possesses two EF-hand calcium-binding sites (helix-loop-helix structures) [18]. Under certain conditions (e.g., high calcium concentration), it can form a heterotetramer (S100A8/S100A9), which is more stable and functionally active, while the homodimer exists very little because of its stability [19]. It is this structure that allows S100A8/A9 to exert its multifunctional extracellular and intracellular activities.

3. Origin and Expression of S100A8/A9

S100A8 and S100A9 are mainly derived from immunocytes, such as neutrophils and macrophages. These proteins are highly expressed intracellularly in these cells, forming stable S100A8/A9 heterodimers, and they participate in inflammatory processes, especially during acute events such as myocardial infarction (MI) [20]. S100A8 and S100A9 proteins comprise approximately 45% of the cytoplasmic proteins in neutrophils. Under physiological conditions, there is sufficient storage of S100A8/A9 in neutrophils and myeloid-derived dendritic cells, while low levels of S100A8/A9 are constitutively expressed in monocytes [21].

S100A8/A9, similar to other members of the S100 protein family, is situated at a chromosomal region known for its variability, 1q21, where a distinct S100 gene cluster is formed and is primarily associated with myeloid cells, particularly neutrophils and monocytes/macrophages [22].

S100A8/A9 expression is upregulated during trauma, infection, heat, stress, and many other inflammatory processes, contributing to the recruitment and activation of immune cells at sites of tissue injury, including the ruptured plaque in coronary arteries during acute MI [23].

The human S100A8/A9 proteins are encoded with distinct amino acid compositions; S100A8 comprises 93 amino acids and has a molecular weight of 10.8 kDa, whereas S100A9 is made up of 113 amino acids and weighs 13.2 kDa [24].

These proteins form various structures such as homodimers, heterodimers (calprotectin), and tetramers, with heterodimer formation being vital for their biological activity, leading to a preference for the formation of S100A8/A9 heterodimer complexes, which are the predominant form of S100A8/A9 in physiological settings [25].

These complexes, referred to as calprotectin, possess multiple biological characteristics.

When Ca^{2+} concentration reaches a certain threshold, S100A8/A9 heterodimers form (S100A8/A9) tetramers, a configuration that is vital for their biological activity [18]. Fig (2)

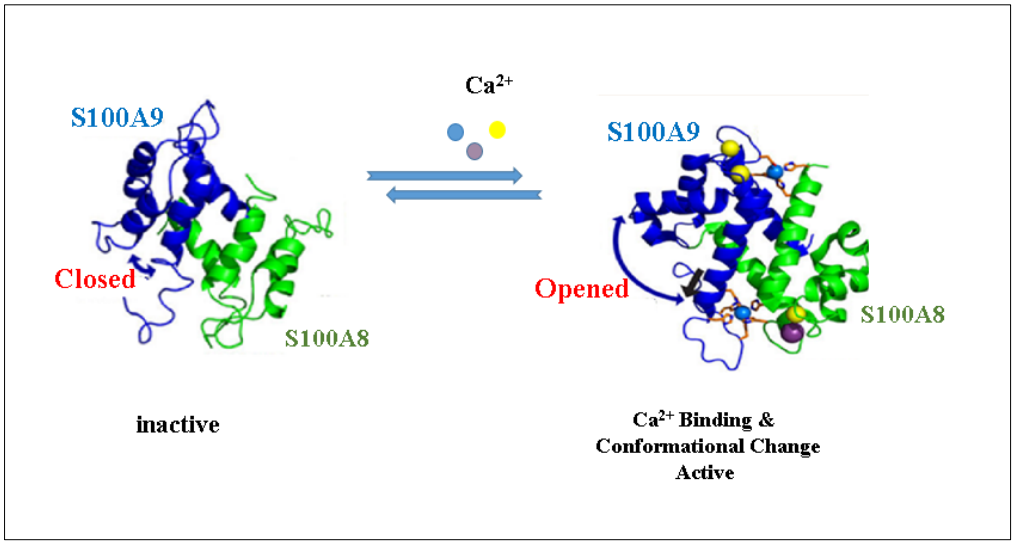

Figure 2: Ca^{2+}-dependent conformational switching of the S100A8/S100A9 heterodimer. In the absence of Ca^{2+}, the S100A8/S100A9 dimer remains closed; Ca^{2+} binding triggers α-helix rearrangement, forming heterotetramers (calprotectin) capable of metal binding and immune functions [18]

Secreted mainly by immune cells such as dendritic cells, neutrophils, monocytes, and activated macrophages, these proteins participate in the pathophysiology of various inflammatory conditions by attracting leukocytes and modulating the inflammatory response to vascular injury. [26].

4. Biological Functions of S100A8/A9 in Myocardial Infarction

4.1 Intracellular Roles

Intracellularly, S100A8/A9 proteins function as calcium-binding cytosolic mediators that regulate various cellular processes [27].

In many cases, S100A8/A9 is suggested to be a Ca^{2+} sensor, which, on binding to Ca^{2+}, changes its structure to expose interaction sites, and in this state, it can interact with various target proteins, changing their activity [28].

S100A8/A9 are highly expressed and can influence intracellular signaling pathways, including the regulation of reactive oxygen species (ROS) production through interaction with intracellular receptors; they perform protective intracellular functions, especially in activated immune cells subjected to elevated inflammatory and metabolic demands [29].

When taken as a whole, these intracellular activities establish S100A8/A9 as a crucial molecular connection between cytoskeletal dynamics, inflammatory signaling pathways, and Ca^{2+} signaling [30].

4.2 Extracellular Roles

In situations related to cell damage and/or activation, S100 proteins can be released into the extracellular space and promote various paracrine and autocrine functions such as inflammation, autoimmunity, and also cell proliferation and survival (including neuronal survival and extension) [31].

S100A8/A9 heterocomplexes usually act as a Damage-Associated Molecular Pattern (DAMP), activating Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) signaling pathways after release under stress conditions or tissue damage by activated phagocytes at local sites of inflammation [15-32].

This triggers downstream signaling cascades that amplify inflammation through cytokine release (e.g., IL-1β) and reactive oxygen species (ROS) generation, both of which are central to myocardial ischemia–reperfusion injury [33]. Figure (3)

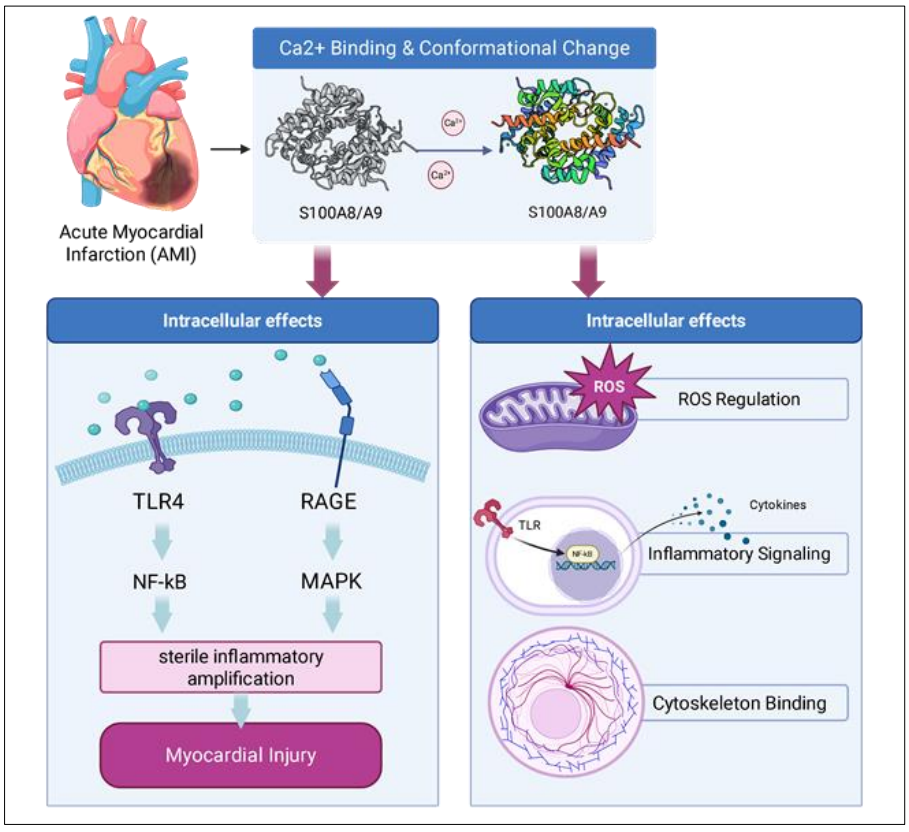

Figure 3: S100A8/A9-Mediated Crosstalk between Calcium Signaling, Oxidative Stress, and Innate Immunity in Acute Myocardial Injury. Created in BioRender. https://BioRender.com/ed5fl6g

5. S100A8/A9 Complex in the Pathophysiology of AMI

Accumulating experimental evidence indicates that the S100A8/A9 heterodimer plays a pivotal pathological role in ischemia and ischemia–reperfusion injury [34-36]. The complex contributes to the pathogenesis of AMI by amplifying sterile inflammation through engagement with pattern recognition receptors, including Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) of various cell types, activating NFκB and mitogen-activated protein kinase (MAPK) pathways [37]. The activation of these signaling cascades leads to recruitment of more inflammatory cells, induction of inflammatory cytokines and chemokines, and an increased synthesis of proteases and extracellular matrix (ECM) proteins [38]. S100A8/A9 binding to RAGE on cardiomyocytes in sepsis can lead to cardiomyocyte dysfunction due to a decrease in cardiomyocyte contractility caused by reduced calcium flux [39]. By delivering AA to the NADPH oxidase complex, intracellular S100A8/A9 might cause oxidative bursts in myeloid cells and exacerbate inflammation [40]. Mitochondrial dysfunction and oxidative stress can cause cardiomyocyte death. S100A8/A9 directly induces mitochondrial dysfunction by suppressing mitochondrial complex I activity [36]. S100A8/A9 interacts with the NADPH oxidase (Nox) complex by binding to p67phox and Rac in neutrophils, thereby promoting oxidative stress [41]. Figure (4)

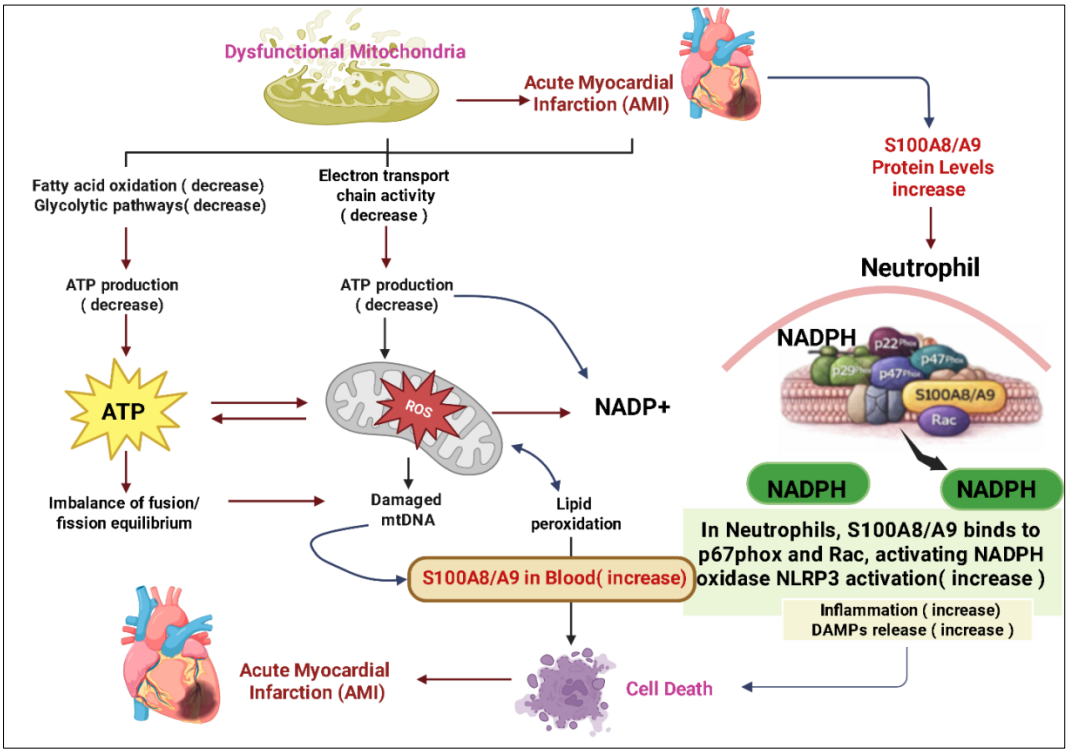

Figure 4: Mitochondrial dysfunction and myocardial infarction dynamics: Acute myocardial infarction (AMI) causes mitochondrial dysfunction characterized by compromised oxidative metabolism, diminished ATP synthesis, and increased mitochondrial reactive oxygen species (ROS) production. Mitochondrial damage induces cardiomyocyte apoptosis and the secretion of damage-associated molecular patterns (DAMPs), such as S100A8/A9. Increased levels of circulating S100A8/A9 amplify innate immune activation through NADPH oxidase-dependent mechanisms in neutrophils, exacerbating oxidative stress and sterile inflammation and advancing cardiac damage. Created in BioRender. https://BioRender.com/2f8edln

Human cardiovascular risk is thought to be indicated by plasma levels of S100A8/A9. S100A8/A9 plasma levels in healthy individuals are predictive of the risk of subsequent cardiovascular events, and S100A9 expression rises prior to STEMI [38].

Because S100A8/A9 levels are elevated in the systemic circulation prior to other markers of cardiac necrosis, they may be a mediator and early biomarker of ACS5.

Patients who experienced cardiovascular mortality or MI after 30 days in the Pravastatin or

Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction [22]. (PROVE IT-TIMI 22) study[46] showed greater median S100A8/A9 levels than those who did not experience any recurrent events. Consequently, raised S100A8/A9 levels demonstrated a markedly higher risk of MI or cardiovascular mortality [5].

6. Clinical Relevance and Biomarker Potential

Higher levels of S100A8/A9 (calprotectin) protein in the blood or serum have been connected to larger infarct size, changes in the anatomy of the left ventricle, and a higher risk of heart failure after an acute myocardial infarction [42].

This protein interacts with receptors such as TLR4 and RAG to promote neutrophil/monocyte recruitment, oxidative stress, mitochondrial dysfunction, and pro-inflammatory signaling, all of which are associated with poorer outcomes following myocardial infarction [43].

Mechanistically, calprotectin causes gene expression by turning on inflammatory pathways through receptors like TLR4 and RAGE. This leads to more pro-inflammatory cytokines being made (like IL-6 and TNF-α) [44].

Elevated plasma or serum concentrations of S100A8/A9 have been associated with larger infarct sizes, adverse left ventricular remodeling, and an increased risk of heart failure following acute myocardial infarction (AMI). Proteomic analyses of post-myocardial infarction patient cohorts demonstrate that the incorporation of S100A8/A9 measurements alongside traditional cardiac biomarkers, including cardiac troponins, BNP/NT-proBNP, and high-sensitivity C-reactive protein (hs-CRP), significantly enhances prognostic accuracy and risk stratification relative to the use of conventional markers in isolation.

For example, a large observational study found that higher levels of circulating S100A8/A9 were linked to post-AMI heart failure. Adding S100A8/A9 to standard risk models made it easier to predict bad outcomes than using traditional biomarkers alone [43].

S100A8/A9 enhances risk classification beyond conventional biomarkers and permits early identification of inflammatory activation after myocardial infarction. Its usefulness as a prognostic marker and possible therapeutic target is supported by the substantial correlation between changes in its circulating levels following reperfusion and unfavorable ventricular remodeling and subsequent heart failure.

Acute myocardial infarction (AMI) is a significant cardiovascular incident caused by the sudden cessation of coronary blood flow, resulting in myocardial ischemia, oxygen deficiency, and irreparable damage to cardiomyocytes [45]. This process is typically begun by the rupture or erosion of an atherosclerotic plaque, leading to thrombus development and acute arterial occlusion [46]. The advancement and evolution of acute myocardial infarction (AMI) are significantly affected by recognized cardiometabolic and lifestyle-associated risk factors, such as dyslipidemia, diabetes mellitus, obesity, hypertension, smoking, older age, male gender, and a familial predisposition to coronary artery disease. Due to the significant morbidity and mortality linked to AMI, prompt identification and precise risk assessment are essential factors influencing patient outcomes [47].

In contemporary clinical practice, cardiac biomarkers—especially cardiac troponins—constitute the foundation for the diagnosis, risk evaluation, and treatment decisions regarding acute myocardial infarction (AMI) [48]. Nonetheless, these indicators mostly indicate downstream myocardial necrosis and offer restricted understanding of the upstream inflammatory mechanisms that significantly affect infarct expansion, ventricular remodeling, and long-term outcomes. This constraint has stimulated growing interest in inflammatory mediators that can detect early innate immune activation after ischemia injury.

Subsequent to coronary occlusion and reperfusion, neutrophils swiftly infiltrate the ischemic myocardium and release significant amounts of the S100A8/A9 heterodimer, thereby enhancing early inflammatory signaling via Toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE)-mediated pathways [28, 49]. Growing data substantiates the significance of S100A8/A9 as a dependable prognostic biomarker, with heightened circulating levels consistently linked to negative cardiac outcomes and an elevated risk of recurrent ischemia episodes [50, 51].

The current findings substantiate this notion by illustrating that circulating S100A8/A9 delivers significant prognostic insights for heart failure advancement post-AMI, providing additional predictive value beyond established biomarkers like cardiac troponin I and B-type natriuretic peptide (BNP). Unlike traditional biomarkers that mainly signify myocardial necrosis or hemodynamic stress, S100A8/A9 indicates the extent of the initial innate inflammatory response, a crucial factor in post-infarction ventricular remodeling [52, 53]. This distinction is clinically significant, as inflammation serves as a precursor to maladaptive structural and functional alterations in the heart.

7. DISCUSSION

In accordance with this biological explanation, the inclusion of S100A8/A9 in predictive models leads to improved discrimination in receiver operating characteristic (ROC) analyses, as well as notable enhancements in risk reclassification and model calibration. These findings underscore the ability of S100A8/A9 to identify high-risk patients who may be insufficiently categorized by traditional clinical and biochemical metrics alone [54].

Mechanistically, these data are biologically credible, as S100A8/A9 acts as a prototypical damage-associated molecular pattern (DAMP) mainly secreted by activated myeloid cells in response to ischemic tissue damage. S100A8/A9 enhances sterile inflammatory responses by activating TLR4 and RAGE signaling pathways, leading to increased cytokine production, oxidative damage, and prolonged immune activation [55, 56]. This inflammatory environment is crucial in infarct growth, fibrotic remodeling, and the subsequent onset of heart failure after acute myocardial infarction (AMI) [57].

The data collectively indicate that S100A8/A9 serves not only as a surrogate measure of injury severity but also as a comprehensive indicator of pathogenic inflammatory activity. This combination biomarker–mediator function highlights its potential use in enhanced post-AMI risk assessment models and endorses its suitability as a future therapeutic target for mitigating inflammation-induced cardiac dysfunction [5].

The data presented here highlight the crucial role of the S100A8/A9 heterodimer in both the inflammatory and reparative stages after acute myocardial infarction (AMI). S100A8/A9, sometimes referred to as calprotectin, is a calcium- and zinc-binding complex primarily generated by activated neutrophils and monocytes/macrophages in response to myocardial damage and inflammatory cardiac conditions [58]. Increased circulation levels have been associated with plaque susceptibility and a heightened risk of atherothrombotic events, underscoring its significance in cardiovascular disease. In addition to chronic atherosclerosis [59], S100A8/A9 increases shortly after acute myocardial infarction (AMI), primarily indicating the acute activation of innate immune cells, so reinforcing its significance as a sensitive marker of inflammatory dynamics that influence long-term cardiac outcomes [60].

8. CONCLUSION

In conclusion, the deregulation of cardiac S100 proteins—especially S100A8/A9—constitutes a pivotal element of the inflammatory response to acute myocardial infarction. In addition to its role as a circulating biomarker, S100A8/A9 serves as a crucial molecular mediator connecting innate immune activation to myocardial damage, maladaptive ventricular remodeling, and tissue repair. Clarifying the context-dependent functions of S100A8/A9 signaling may consequently enhance biomarker-guided risk stratification and facilitate the creation of specific anti-inflammatory approaches to improve post-infarction outcomes.

Conflict of Interest: There is no conflict of interest among the authors.

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