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Research Article

Scientific Evidence on the Involvement of the Proteins ICAM1, PCSK9, NGAL, and MMP9 in the Progression of Endothelial Dysfunction. A Systematic Review and Epistemic Meta-Analysis

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Abstract

Introduction: Cardiovascular diseases (CVD) constitute the leading cause of death worldwide. It is documented that obesity, dyslipidemia, diabetes mellitus, and hypertension, all of which are components of the metabolic syndrome, constitute high-risk factors for the development of CVD. Because the prevalence of these components is sufficiently high, various studies have focused on identifying biomarkers associated with the occurrence of these metabolic alterations and endothelial dysfunction. Given their roles in endothelial activation, lipid regulation, and extracellular matrix degradation - fundamental processes in the progression of acute coronary syndrome (ACS) - we focus on four key proteins: ICAM-1, PCSK9, NGAL (also known as lipocalin-2), and MMP-9.
Therefore, this study aims to identify scientific evidence studying the role of these biomarkers in endothelial pathophysiology and the variations in their serum concentrations in patients with metabolic syndrome undergoing percutaneous coronary intervention (PCI).

Methods: To achieve this, we conducted a systematic literature search in PubMed, Web of Science, and BIREME databases, following the PICO strategy and PRISMA guidelines.

Results: A total of 53 articles with a methodological quality score ≥60% were included. We organized the evidence into thematic axes to integrate heterogeneous findings and assess the scientific coherence of the mechanisms underlying endothelial dysfunction. From this analysis, our results showed that ICAM-1 correlates with endothelial activation driven by a proinflammatory state and with the occurrence of major adverse cardiovascular events (MACE); PCSK9 is associated with elevated LDL serum concentrations and endothelial cell apoptosis, whereas NGAL and MMP-9 act synergistically in extracellular matrix degradation and atherosclerotic plaque instability. Notably, no studies have simultaneously evaluated all four proteins in patients with metabolic syndrome undergoing PCI, revealing a gap in clinical and molecular knowledge.

Conclusions: Therefore, taken together, these biomarkers emerge as early predictors of cardiovascular risk and represent potential tools for preventive and personalized vascular risk stratification in patients with metabolic syndrome.

Keywords: Metabolic syndrome, Endothelial dysfunction, Biomarkers. ICAM-1, PCSK9, NGAL, MMP9.

Abbreviations

ACS: Acute Coronary Syndrome
AGEs: Advanced Glycation Ends
AKI: Acute Kidney Injury
AMI: Acute Myocardial Infarction
ApoE: Apolipoprotein E
API: Atherogenic Index of Plasma
AUC: Area Under the Curve
CABG: Coronary Arterial Bypass Grafting
CAD: Coronary Arterial Disease
CAT: Catalase
CCL2: C-C motif ligand 2
CHD: Chronic Heart Disease
CRP: C Reactive Protein
CVD: Coronary Vascular Diseases
ELISA: Electro Immuno Absorbent Assay
FGF-23: Fibroblast Growth Factor 23
Gpx: Glutathione peroxidase
HDL-c: High Density Lipoprotein-c,
HF: Heart Failure
HFmrEF: Heart failure with reduced Ejection Fraction
HR: Hazard Ratio
HsCRP: Human soluble C Reactive Protein
ICAM-1: Intracellular Adhesion Molecule 1
IHF: Ischemic Heart Failure
ICAM-1: Intracellular Adhesion Molecule 1
IL-1β: Interleukin-1 beta
IL-6: Interleukin-6
ISR: In-stent restenosis
LDL: Low Density Lipoprotein
LDL-c: Low Density Lipoprotein-cholesterol
LVEF: Left Ventricular Ejection Fraction
MACE: Major Adverse Cardiovascular Events
MAD: Malonylaldehyde
MCP1: Monocyte Chemotactic Protein 1
MI: Myocardial Infarction
MMP2: Matrix Metalloprotease 2
MMP9: Matrix Metalloprotease 9
MS: Metabolic Syndrome
NGAL: Neutrophil Associated Lipocalin
NSTEMI: Non-elevated ST-segment Elevation Myocardial Infarction
NT-pro BNT: N-terminal Pro B Type Natriuretic protein
OCN: Osteocalcin
OR: Odds Ratio
PAD: Peripheral Artery Disease
PCI: Percutaneous Coronary Intervention
PCSK9: Proprotein Convertase Subtilisin/Kexin type 9
sLOX-1: Soluble Lectin-like Oxidized low density lipoprotein receptor 1
STEMI: ST-segment Elevation Myocardial Infarction
SOD: Superoxide Dismutase
TG: Triglycerides
T2DM: Type 2 Diabetes Mellitus.
TNFα: Tumor Necrosis Factor alpha
VAI: Vascular Adiposity Index.
VCAM-1: Vascular Cell Adhesion Molecule 1.

Introduction

Metabolic syndrome (MS) comprises a cluster of risk factors linked to cardiovascular disease. These risk factors include abdominal obesity, insulin resistance, hypertension, impaired glucose metabolism, and dyslipidemia. Together, these conditions generate a proinflammatory state and oxidative stress, leading to hemodynamic dysfunction and ischemia [1].

Globally, about 31.4% of adults are affected by (MS), meaning that over one billion people live with this condition [2]. A meta-analysis including 1,129 prevalence datasets from over 28 million participants found global MS rates ranging from 12.5% to 31.4%, with the highest prevalence in the Eastern Mediterranean and the Americas, increasing alongside national income levels [3].

Addressing these conditions is critical. According to World Health Organization (WHO) data, in 2022, approximately 111,774 deaths associated with diabetes [4] and 231,247 deaths from cardiovascular disease occurred among adults aged 25 years and older [5]. Since mortality due to cardiovascular disease surpasses that of diabetes, the early identification of symptoms related to cardiovascular pathologies is of the utmost importance. The latter enables timely treatment and reduces mortality.

Endothelial dysfunction is a crucial step in the development of atherosclerosis. It worsens with classic risk factors such as hypertension and hypercholesterolemia, which trigger proinflammatory endothelial activation [6]. This activation leads to the release of adhesion molecules, mainly intercellular adhesion molecule-1 (ICAM-1). Elevated ICAM-1 promotes leukocyte adhesion and migration into the vascular intima, a key step in plaque formation. Its cleavage generates soluble ICAM-1 (sICAM-1), directly associated with subclinical atherosclerosis, including coronary artery calcification. Acting as a mediator of monocyte recruitment, sICAM-1 amplifies vascular inflammation and accelerates the progression of cardiovascular disease [7].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a crucial role in regulating blood lipid levels. It degrades the low-density lipoprotein receptor (LDLR), which removes LDL cholesterol from the blood. By lowering LDLR expression, PCSK9 increases cholesterol levels [8]. Additionally, PCSK9 contributes to endothelial dysfunction by promoting inflammation through multiple mechanisms. These include signaling endothelial cell death (apoptosis), weakening blood vessel stability, increasing the expression of molecules such as ICAM-1 that attract immune cells, and elevating levels

of chemotactic factors, including MCP-1 and MCP-3, that promote further immune cell recruitment to atherosclerotic plaques. These combined processes exacerbate inflammation in blood vessels and increase the risk of cardiovascular disease [9].

Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a key biomarker of vascular inflammation. Although studies in stable coronary artery disease remain limited, elevated NGAL levels have been identified as independent predictors of mortality and major adverse cardiovascular events in patients with acute myocardial infarction [10]. Its relevance increases through direct interaction with matrix metalloproteinase-9 (MMP-9), a critical enzyme in extracellular matrix degradation, which is strongly linked to atherosclerotic plaque instability [6]. NGAL stabilizes MMP-9 by forming a complex that prevents its degradation, thereby prolonging its half-life and proteolytic activity. Therefore, NGAL is a more robust marker than MMP-9 alone in the context of coronary artery disease [10].

As for MMP-9, it is directly involved in endothelial dysfunction through multiple pathways, including inflammatory cell migration into the arterial wall, endothelial apoptosis, and responses to LDL oxidation. Elevated MMP-9 levels have been consistently associated with unstable, lipid-rich plaques, underscoring their role as a marker of rupture risk and adverse cardiovascular events [6].

Given the crucial role of these proteins in the pathophysiological mechanisms of endothelial dysfunction and atherosclerosis, particularly in the context of coronary artery disease, and considering their high prevalence worldwide, as well as the associated morbidity, mortality, and public health costs, it is a priority to deepen our understanding of the involvement of ICAM-1, PCSK9, NGAL (lipocalin-2), and MMP-9 in patients with metabolic syndrome undergoing coronary intervention. The aim is to assess their potential as early markers of endothelial dysfunction, thereby strengthening preventive and personalized cardiovascular medicine, with an emphasis on risk stratification and timely intervention.

To this end, we formulated the following research question: What is the current state of the art regarding endothelial pathophysiology associated with changes in serum concentrations of ICAM-1, PCSK9, NGAL, and MMP-9 in patients with metabolic syndrome undergoing coronary intervention? To address this question, we conducted a systematic review of scientific literature. Then we performed an epistemic meta-analysis to identify, synthesize, and critically evaluate the available evidence on the association between these biomarkers and endothelial dysfunction and myocardial impairment.

Materials and Methods

We conducted a systematic review on February 19, 2025, following the PICO (Participants, Intervention, Comparison, and Outcomes) strategy and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach. We subsequently evaluated the selected articles and conducted an epistemic meta-analysis. Based on the above and in accordance with the PICO strategy, the search was as follows:

PICO Strategy

In patients diagnosed with metabolic syndrome (Participants) undergoing coronary intervention, either stenting or angioplasty (Intervention), Is there a variation in serum concentrations of ICAM-1, PCSK9, LIPOCALIN 2, and MMP9 (Comparison) in the four weeks following the procedure, in terms of variability, sensitivity test, ROC curve, statistical significance, or specificity (Outcome)?

Databases and Search Strategy

Utilizing the strategy described above and incorporating Medical Subject Headings (MeSH) terms, the search employed the Boolean operators "AND" and "OR." The "AND" operator ensured the simultaneous presence of specific terms, while the "OR" operator included related concepts. We searched three electronic databases: PubMed, developed by the US National Library of Medicine (NLM), which comprises over 38 million citations and serves as a global resource for health-related information; Web of Science (WOS), a comprehensive platform that grants access to bibliographic and supplementary databases; and BIREME, the virtual health sciences library of Latin America and the Caribbean. BIREME is recognized as the most exhaustive database in the region.

Definition of PICO Components and Search Terms for the Research Question:

Participants: we included articles on patients with metabolic syndrome or cardiac comorbidities, using the following terms with "Patients" and the Boolean operators' AND' and 'OR':

- Patients
- Diabetes Mellitus
- Metabolic Syndrome
- Atherosclerosis
- Endothelial Dysfunction
- Cardiovascular Complications
- Heart Injury
- Heart Failure

Intervention: Articles mentioning any coronary intervention using the Boolean operator "OR".

- Coronary Stents
- Angioplasty
- Coronary Intervention

Comparison: Studies reporting serum concentrations of the following proteins and their acronyms:

- ("Neutrophil Gelatinase-Associated Lipocalin" OR "NGAL" OR "Lipocalin-2")
- ("Intercellular Adhesion Molecule 1" OR "ICAM-1")

- ("Proprotein Convertase Subtilisin/Kexin Type 9" OR "PCSK9")
- ("Matrix Metalloproteinase-9" OR "MMP-9")

Outcome: Articles evaluating the clinical relevance of the variation in serum concentrations, using the following terms:

- Serum concentration variability
- Sensitivity Assay
- ROC curve
- Statistical significance
- Specificity

We obtained a large number of scientific articles, many of which addressed unrelated pathologies not relevant to our research question.

Therefore, we decided to use the following inclusion and exclusion criteria:

Inclusion Criteria

- Patients over 18 years of age.
- Diagnosis of metabolic syndrome according to the WHO.
- Patients with diabetes mellitus, dyslipidemia, and/or systemic arterial hypertension.
- Clinical trials, observational studies (cohorts, case-controls, cross-sectional studies).
- Systematic reviews and meta-analyses with relevant data.
- Articles in English or Spanish.

Exclusion Criteria

- Letters to the editor, comments, conference abstracts.
- Studies with small samples, low methodological quality, or inadequate statistics.
- Duplicate studies without additional information.
- Patients without a clear diagnosis of metabolic syndrome.

This strategy provided a comprehensive narrative that synthesized key findings on the pathophysiology of metabolic syndrome and its cardiac comorbidities, highlighting its impact on endothelial dysfunction and progression to acute coronary syndrome.

The results were recorded and organized in Mendeley Reference Manager (https://www.mendeley.com/reference-management/reference-manager). This process was repeated for Web of Science and BIREME, eliminating duplicate articles.

Evaluation using the PRISMA method

From the articles stored in Mendeley, we selected those that could provide us with information to answer our research question. We therefore decided to evaluate the quality of the included studies according to the PRISMA criteria, considering:

1. Clarity in research objectives.
2. Research question consistent with the objectives.
3. Robust methodology.
4. Definition of parameters relevant to our research question, such as metabolic syndrome undergoing coronary intervention, ICAM-1, PCSK9, NGAL, MMP-9, comparators, and outcomes related to endothelial dysfunction.
5. Results aligned with the objectives.

We weighed each criterion from 0 to 20%, and we only included those articles that achieved a score of 60% or higher in the meta-analysis.

Epistemic Meta-Analysis

Epistemic meta-analysis is a process of reviewing, comparing, and critically synthesizing different pieces of knowledge to evaluate their strength, limitations, biases, and consistency. Due to the results obtained in the systematic review, we opted to perform it because of the heterogeneity in their designs (cross-sectional, prospective, observational, experimental, or systematic reviews), in the characteristics of the population (inclusion criteria, age ranges, presence of comorbidities), and in the biomarkers used. In addition, several of the available studies do not report the statistical results necessary for inclusion in a rigorous quantitative meta-analysis. The aim is to integrate knowledge from studies that use different metrics, grouping them into comparable thematic areas, thus enabling the construction of a critical and orderly synthesis of the evidence.

Results

The state of the art on the association of biomarkers with endothelial dysfunction.

We conducted a systematic review using the PICO strategy and the PRISMA approach, resulting in a decision tree that progressively narrowed down the research question, utilizing established components.

During the search and selection process, we did not identify any studies that thoroughly answered the question posed, as defined by the PICO criteria. In the initial stage, we retrieved 29,137 articles for the Participants' dimension and 132,924 records for the Intervention dimension. For the Comparison dimension, when combining the proteins of interest with the MeSH term "Serum Concentration," we retrieved the following numbers of articles: 79 for NGAL, 264 for MMP-9, 382 for ICAM-1, and 24 for PCSK9. Regarding the Outcomes dimension, the search returned 4,985,137 results.

However, when integrating the P and I components, the search only retrieved 1,110 articles. Subsequently, when adding the C component, the result was zero, which remained unchanged when all four components of the PICO model were searched.

Application of the PRISMA approach: from the universe of articles to the final screening.

We chose to include articles that considered patients with metabolic syndrome as part of the pathophysiological progression towards cardiovascular disease and acute coronary syndrome.

From the three databases and using the search parameters established according to the PICO strategy and the PRISMA approach described above, we retrieved 771 records. Of these, we eliminated 183 duplicates and 462 that were not relevant to the research question.

Subsequently, of the 91 full-text articles evaluated for eligibility, 46 were excluded for failing to meet the quality criteria, leaving 45 studies. In addition, we manually selected nine relevant articles to cover the key proteins related to the research question, bringing the total to 53 studies (Figure 1).

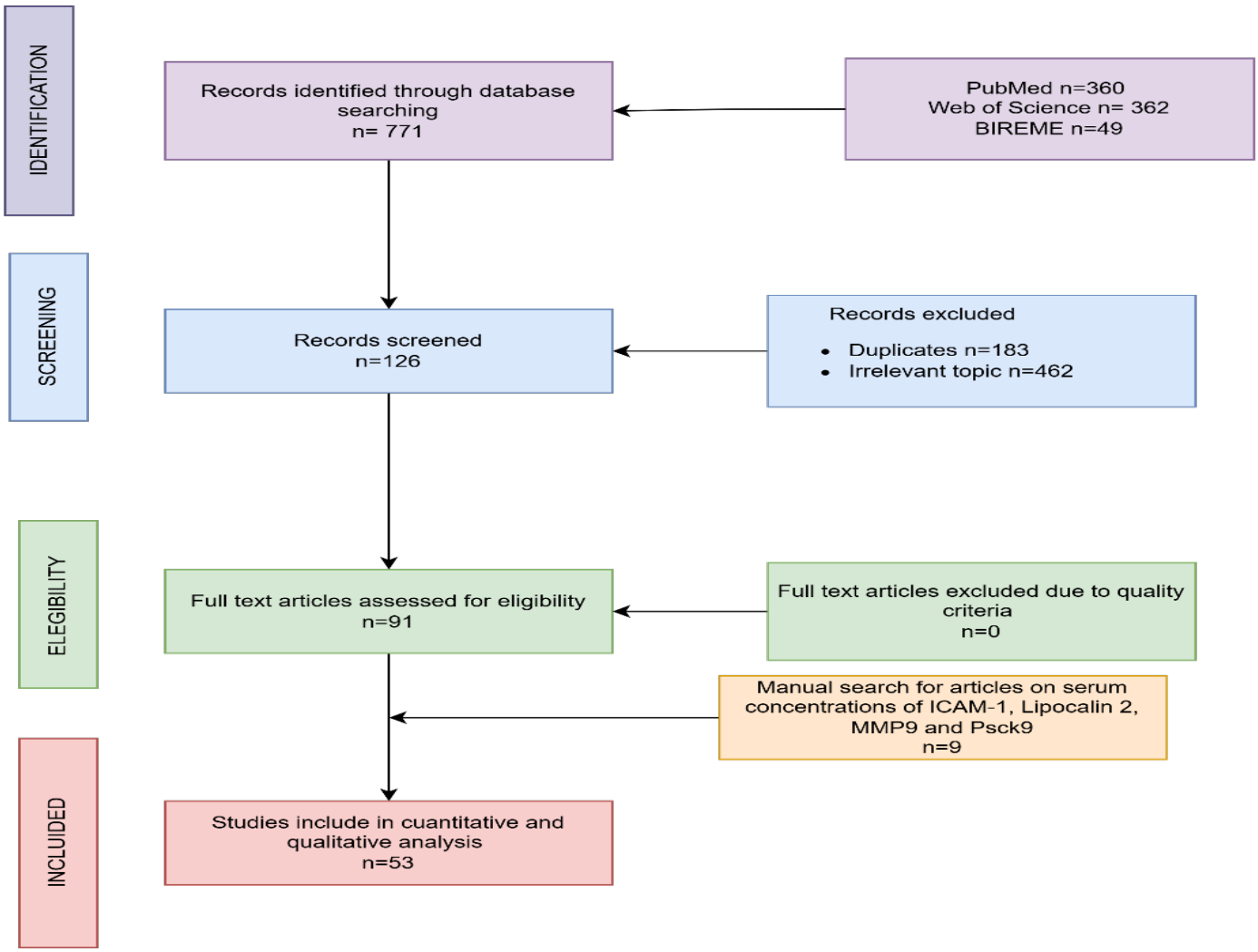

Figure1: Flow diagram describing how we employed the PRISMA method to answer the research question. It visually represents the process of narrowing down the initial search to a rigorous selection of high-quality studies relevant to the review's objective.

Hyperglycemia and endothelial dysfunction: role of inflammatory biomarkers and hematological indices.

Diabetes mellitus is one of the main risk factors for the development and progression of coronary artery disease, conferring a worse clinical prognosis after acute coronary syndrome or percutaneous coronary intervention. Several recent studies have explored the role of inflammatory and metabolic biomarkers in this context, demonstrating significant associations with clinical outcomes, which supports the need to investigate new molecules with potential prognostic value, including ICAM-1, PCSK9, MMP-9, and NGAL.

Although none of the reviewed studies explicitly quantified serum levels of ICAM-1, PCSK9, MMP-9, or NGAL, approximately one-fifth addressed the role of inflammatory biomarkers in the pathophysiology and prognosis of patients with acute coronary syndrome and diabetes mellitus. In this context, it has been reported that in-stent restenosis is a consequence of persistent vascular inflammation and endothelial dysfunction, mediated by cytokines such as TNF-α, IL-6, IL-1β, and acute phase markers such as hsCRP, all of which are linked to the activation of endothelial adhesion molecules similar to ICAM-1, which are key in leukocyte migration and

the progression of atherosclerosis [11]. Likewise, vascular biomarkers, such as Big ET-1, and composite lipid parameters, including the plasma atherogenic index, demonstrated substantial prognostic value for predicting major adverse cardiovascular events (MACE) in this patient group [12].

Hematological inflammation markers, including AISI, SIRI, and NLRP, emerged as complementary tools for risk stratification and characterization of more aggressive inflammatory profiles [13]. Some studies have shown that rigorous glycemic control (HbA1c < 6.5%) may increase the risk of long-term MACE, whereas moderate control, accompanied by adequate lipid reduction, offers a safer balance for secondary prevention [14].

Taken together, this evidence supports the hypothesis that the interaction between chronic inflammation, endothelial dysfunction, and metabolic alterations plays a central role in clinical progression and opens the door to exploring the prognostic value of proteins such as ICAM-1, PCSK9, MMP-9, and NGAL in this context (Table 1).

Authors, year of publication	**Study Type**	**Study Model**	**Study Population**	**Proteins Measured and Quantification Method**	**Statistical Data**	**Relation to the Research Question**	**PRISMA Quality Rating**
Jarrah, et al., (2020)	Post hoc analysis	Humans	2,426 Jordanian patients who underwent PCI	No specific protein biomarkers were measured	Multivessel reintervention: 38.2% in non-smoking diabetics ($p < 0.001$). Higher in-hospital mortality in non-smoking diabetics (1.8%) compared with smokers (0.4%, $p = 0.006$)	Non-smoking diabetic patients exhibit greater severity of coronary artery disease and worse post-PCI clinical outcomes.	80%
Jin, et al., (2020)	Prospective observational cohort study	Humans	4,381 patients with CAD.	c-LDL.	HR for MACE in the highest tertile of LDL-TG + T2DM: 2.212 ($p < 0.001$)	Elevated LDL-TG levels are associated with an increased risk of MACE in patients with stable CAD and T2DM or prediabetes.	80%
Ma, et al., (2020)	Retros spective cohort study.	Humans	798 T2DM patients undergoing PCI	AIP (Atherogenic index of plasma) (log [TG/HDL-C])	High AIP at admission was associated with an increased risk of MACE in T2DM patients with ACS undergoing PCI.	The AIP is a strong independent predictor of MACE in T2DM patients with ACS undergoing PCI.	90%
Bhat, et al., (2021)	Systematic review.	N/A	N/A	Non-specific protein biomarkers measured	29% of diabetic patients undergoing Coronary artery bypass grafting (CABG) experienced MACE vs 46.5% in those undergoing PCI ($p < 0.01$).	CABG is the preferred revascularization strategy in patients with stable CAD and type 2 diabetes mellitus (T2DM), due to its association with better long-term outcomes.	70%

Cui, et al., (2021)	Systematic review.	N/A	N/A	Non-specific protein biomarkers measured	Recurrence of MI in T2DM patients exceeds 40%. In Asia, T2DM patients have an 89% higher risk of mortality compared to non-diabetics.	T2DM is a significant risk factor for MI development and recurrence and worsens prognosis.	80%
Jakubiak, et al., (2021)	Systematic review.	N/A	N/A	TNF-α, IL-6 and IL-1β	Prevalence of PAD in diabetic patients over 40 years is estimated at 20%, with T2DM associated with greater PAD severity.	T2DM is a risk factor for ISR due to chronic inflammation, endothelial dysfunction, platelet dysfunction, hypercoagulability, and vascular smooth muscle cell proliferation.	90%
Kim, et al., (2021)	Observational study	Humans	13,104 patients with AMI	Non-specific protein biomarkers were measured	Mortality of T2DM: 21.1% in men and 21.5% in women (p = 0.813)	Among patients with T2DM and AMI, no differences in mortality rate or MACE were observed between men and women.	80%
Li, et al., (2021)	Retrospective cohort study with 3-year follow-up.	Humans	377 patients with ACS and HFmrEF undergoing PCI (132 with T2DM).	HbA1c	Event incidence: 96.1 vs 44.6 per 1000 person-years (T2DM vs non-T2DM)	T2DM is associated with worse outcomes in ACS patients undergoing PCI, increasing the risk of mortality and rehospitalization due to heart failure.	90%
Yang, et al., (2021)	Prospective observational cohort study	Humans	2,877 patients with T2DM + ACS	HbA1c	Higher MACE in patients with HbA1c < 6.5% at 2 years follow-up	Strict glycemic control (HbA1c < 6.5%) two years after PCI is associated with a higher risk of MACE in patients with T2DM and ACS.	80%
Al-Ali, et al., (2022)	Observational study	Humans	Non-diabetic patients hospitalized for STEMI in Basrah, Iraq	Non-specific protein biomarkers were measured.	14.8% had LVEF <55%. Four-week mortality: 13.1%	Insulin resistance predicts worse post-STEMI outcomes, even in the absence of type 2 diabetes mellitus (T2DM).	70%

Babes, et al., (2022)	Systematic review.	N/A	N/A	CRP, Fibrinogen.	25–30% of ACS inpatients have diabetes, along with ACS at a younger age, and have a higher mortality rate.	T2DM significantly increases the risk of ACS development and is associated with worse clinical outcomes due to the pro-inflammatory and pro-thrombotic state.	80%
Fan, et al., (2022)	Retrospective observational study	Humans	Patients with ACS undergoing PCI between 2016 and 2018	Hematological inflammatory indices (AISI, SIRI, NLRP), derived from complete blood count	Higher tertiles of AISI, SIRI, and NLRP were associated with increased MACE ($p < 0.001$)	Hematological inflammatory indices, including AISI, SIRI, and NLRP, may help identify ACS patients undergoing PCI who are at higher risk of MACE.	70%
Li, et al., (2022)	Retrospective cohort study	Humans	2,023 patients with ACS + PCI	Human Sensible C-Reactive Protein (HsCRP)	hsCRP > 1.21 mg/L: associated with higher cardiovascular risk ($p = 0.010$). Association of HbA1c with cardiovascular events observed only in patients with hsCRP ≤ 1.21 mg/L.	hsCRP may influence the relationship between HbA1c and cardiovascular risk in ACS patients after PCI.	80%
Ma, et al., (2022)	Prospective observational study	Humans	1,574 patients with coronary ISR.	Big Endothelin-1 (Big ET-1)	In diabetic patients, Big ET-1 was associated with a 105% increased risk of MACE ($p = 0.001$) and a 98% increased risk of secondary events ($p = 0.002$).	Elevated plasma Big ET-1 levels are associated with worse cardiovascular prognosis in patients with ISR and T2DM.	90%
Jeong, et al., (2023)	Retrospective cohort study.	Humans	26,922 T2DM patients with a history of PCI.	C-LDL	Patients <65 years, risk of repeat PCI and stroke increased with rising LDL-C levels. In ≥65 years, LDL-C between 55–69 mg/dL was optimal for reducing events, and in the overall cohort, this range was associated with lower all-cause mortality	For patients <65 years, LDL-C < 55 mg/dL is recommended; for those ≥65 years, LDL-C between 55–69 mg/dL may be more appropriate to prevent repeat PCI and stroke.	90%

Tampou loglou, et al., (2023)	Systematic review.	N/A	N/A	Non-specific protein biomarkers measured	Significant reduction in mortality between hospitalization and 6 months in patients treated with intravenous insulin to maintain blood glucose between 72–180 mg/dL.	T2DM worsens prognosis in ACS patients; moderate glycemic control is crucial for improving outcomes.	90%
Wei, et al., (2023)	Retrospective cohort study	Humans	Patients with STEMI undergoing PCI	Plasma glucose (ABG, FBS); calculation of SHR (stress hyperglycemia ratio)	Increases in ABG or FBS were associated with a higher in-hospital mortality risk (27% and 25%, respectively; $p < 0.001$)	SHR was significantly associated with a higher risk of in-hospital death and mortality, independent of prior diabetic status.	80%
Jonas, et al. (2024)	Post hoc analysis of a clinical trial	Humans	76 patients with T2DM undergoing PCI with zotarolimus-eluting stents	Serum HbA1c	HbA1c ≥7.5%: neointimal hyperplasia (NIH) 16.1% ± 9.8; HbA1c <7.5%: NIH 12.6% ± 8.0 ($p = 0.01$, univariate)	Glycemic control at the time of PCI was not significantly associated with the development of neointimal hyperplasia at 9 months in diabetic patients treated with zotarolimus-eluting stents	90%
Planchat, et al., (2024)	Systematic review	Nonexperimental	Patients with T2DM who underwent PCI or experienced an ACS.	Non-specific protein biomarkers were measured	Systematic review	The use of high-dosage statins and glucose-lowering agents (GLP-1 RA and SGLT2i) is recommended to improve long-term outcomes	80%
Beena, et al., (2025)	Retrospective cohort study.	Humans	Women presenting with STEMI	Non-specific protein biomarkers were measured.	Higher in-hospital mortality in women with T2DM, higher rates of cardiogenic shock and HF ($p < 0.05$).	Increased in-hospital mortality in women with T2DM	60%

Table1: Studies examining the association between Type 2 Diabetes Mellitus and Coronary Vascular Diseases.

Role of MMP-9 and NGAL in atherosclerosis: Plaque rupture factor.

In relation to dyslipidemia and atherosclerosis, the study by Kook [15] stands out for determining serum concentrations of MMP-9, NGAL, and sLOX-1 in 85 patients with acute coronary syndrome. Notably, the combination of sLOX-1, MMP-9, white blood cell count, and CK-MB achieved an area under the curve of 0.8431, with a sensitivity of 62.2% and specificity of 97.6%, demonstrating high discriminatory value for identifying plaque ruptures.

While Pérez's study [16] included 873 patients with acute coronary syndrome, in which he evaluated the relationship between serum levels of C-reactive protein (CRP) and fibrinogen, the results indicated that there was no significant correlation between CRP and fibrinogen levels and the extent of coronary artery disease ($p = 0.829$ and $p = 0.810$, respectively). However, both biomarkers were associated with a higher rate of adverse cardiovascular events, suggesting

their usefulness in risk stratification, although not as direct indicators of the severity of coronary atherosclerosis.
Likewise, approximately 50% of the articles reviewed included lipid profile measurements to calculate plasma atherogenic indices, which were established as predictors of poor prognosis, associated with the progression of neo-atherosclerosis, the appearance of lesions in non-target vessels, and the incidence of MACE [17] (Table 2).

Authors, year of publication	Study Type	Study Model	Study Population	Proteins Measured and Quantification Method	Statistical Data	Relation to the Research Question	PRISMA Quality Rating
Qin, et al., (2020)	Cohort study.	Humans	2,356 T2DM patients undergoing PCI	AIP (TG and HDL-C)	MACE incidence: 20.5%; AIP as an independent predictor (HR 1.528; p = 0.011); HR 1.614 with propensity score adjustment (p < 0.001).	The AIP is an independent predictor of poor prognosis (higher risk of major adverse cardiovascular events, or MACE) in T2DM patients undergoing PCI.	70%
Tanaka, et al., (2020)	Retrospective study.	Humans	2,190,300 patients.	N/A	Coronary Cerebral Embolism (CCE) incidence: 4.4/10,000; mortality: 11%; risk factors included age, T2DM, stroke, male sex, smoking, heart failure, etc.	CCE is a rare but serious complication of cardiovascular procedures. Atherosclerotic risk factors and specific cardiovascular interventions are associated with increased occurrence.	70%
García Sayan, et al. (2023)	Cross-sectional observational study.	Humans	960 Mexican American adults.	N/A	Among participants >55 years, male sex (OR = 2.4), hypertension (OR = 2.3), and prediabetes (OR = 3.4) were significantly associated with lower fibromuscular dysplasia percentage (%FMD).	Endothelial dysfunction, measured by %FMD, is associated with cardiometabolic risk factors in asymptomatic Mexican American adults.	80%
Pérez Díaz, et al., (2023)	Prospective observational study.	Humans	873 patients diagnosed with ACS.	CRP and fibrinogen.	No significant correlation between CRP and fibrinogen levels and the extent of CAD (p = 0.829 and p = 0.810, respectively).	CRP and fibrinogen levels were not correlated with the extent of coronary atherosclerosis in ACS patients.	80%

Sun, et al., (2023)	Retrospective cohort study	Humans	Patients with IHF undergoing PCI.	TyG index (calculated from TG and fasting glucose)	One-unit increase in TyG index was associated with a 41% increased risk of MACE (HR = 1.41; 95% CI: 1.22–1.62; p < 0.001)	TyG index is an independent positive predictor of MACE in patients with IHF undergoing PCI.	80%
Kook, et al., (2024)	Prospective observational clinical study.	Humans	85 patients with ACS.	sLOX-1, MMP-9, NGAL	sLOX-1: (p < 0.0001). MMP-9: (p = 0.0274). NGAL: (p = 0.0874), not significant. Combined model (sLOX-1, MMP-9, leukocyte count, CK-MB): AUC 0.843 (p < 0.0001); sensitivity 62.2%, specificity 97.6% for plaque rupture detection.	Plasma levels of sLOX-1 and MMP-9 were significantly higher in ACS patients with plaque rupture. NGAL showed no significant difference between rupture and non-rupture groups in this study.	90%
Liu, et al., (2024)	Retrospective cohort study	Humans	769 patients with CAD.	RLP-C (Remnant Lipoprotein Cholesterol).	Optimal cutoff for RLP-C: 0.555 mmol/L; sensitivity 81.4% and specificity 63.7% for predicting non-target lesion progression.	Elevated RLP-C levels are an independent risk factor for non-target lesion progression, even when LDL-C levels are well controlled.	80%
Nakamura, et al., (2024)	Observational study.	Humans	83 patients undergoing PCI for ACS.	Lipoprotein(a), total cholesterol, non-HDL, LDL-C.	T2DM in the neo-atherosclerotic group: 45% vs 17% in the non-neo-atherosclerotic group (p = 0.03). Lp(a) > 30 mg/dL (OR: 11.0; 95% CI: 1.492–81.02; p = 0.02).	Elevated non-HDL cholesterol and Lp(a) are associated with the development of neo-atherosclerosis one year after drug-eluting stent implantation. T2DM was also associated with a higher prevalence of neo-atherosclerosis.	90%

Table2: Studies addressing the association of Type 2 Diabetes Mellitus with Dyslipidemia or Atherosclerosis.

Metabolic syndrome and inflammation: the absence of biomarkers.

Metabolic syndrome is a set of clinical and metabolic disorders that include abdominal obesity, dyslipidemia, hypertension, and glucose intolerance, all of which are associated with an increased risk of coronary heart disease. Its importance lies in promoting a chronic, low-grade inflammatory state and increased oxidative stress, mechanisms that accelerate endothelial damage and the progression of atherosclerosis.

Svarovskaya's findings [18] in patients with MS and acute coronary syndrome, showed significantly higher levels of total cholesterol, triglycerides, LDL-C, and lipoprotein (a), accompanied by an increase in inflammatory mediators such as TNF-α (2.8 times), IL-1 (5 times), and Lp-PLA2 (2.7–5.1 times higher than in controls), as well as endothelin-1 (1.9 to 3.7 times higher). These biochemical changes translated into a worse prognosis: after 1 year of follow-up, the rate of in-stent restenosis was 20.8% in patients with MS compared with 6.3% in those without MS, confirming MS as a determinant of atherosclerotic progression and major adverse cardiovascular events (MACE).

Complementarily, Zhao's study [19] showed that the prevalence of MS in patients with NSTEMI undergoing percutaneous coronary intervention was close to 51%. After one year, patients with MS had significantly more MACE, including death from any cause, hospitalization for heart failure, and recurrent nonfatal myocardial infarction. In addition, a BMI ≥28 kg/m² was identified as an independent predictor of adverse events, with a more marked impact in older adults and patients with LVEF ≤40%.

However, despite the evident association between MS and systemic inflammation, to date, none of these studies have directly evaluated emerging biomarkers such as NGAL, MMP-9, ICAM-1, or PCSK9, whose pathophysiological relevance in vascular remodeling, plaque rupture, and lipid regulation is widely recognized in other clinical settings (Table 3).

Authors, year of publication	Study Type	Study Model	Study Population	Proteins Measured and Quantification Method	Statistical Data	Relation to the Research Question	PRISMA Quality Rating
Svarovskaya, et al. (2020)	Prospective cohort study.	Humans	80 patients with CAD undergoing PCI	hsCRP, IL-6, TNF-α, ICAM-1, and VCAM-1.	Patients with MS showed significantly higher levels of hsCRP, IL-6, TNF-α, ICAM-1, and VCAM-1 ($p < 0.05$). The incidence of MACE was higher in the MS group ($p < 0.05$).	Inflammatory and endothelial dysfunction markers are significantly elevated in CAD patients with MS after PCI and may predict complications and prognosis.	90%
Jakubiak, et al., (2021)	Retrospective observational study	Humans	199 patients with MI undergoing PCI	N/A	The group with MS (68.3%) showed a significantly higher rate of cardiovascular mortality ($p = 0.03$).	MS is highly prevalent among MI patients and is associated with a substantially higher rate of cardiovascular mortality.	80%
Longo, et al., (2021)	Cross-sectional observational study.	Humans	Patients with established atherosclerotic disease.	N/A	The most prevalent risk factors were: -Increased waist circumference (80.2%) -Elevated blood pressure (77.4%) -Elevated fasting glucose (62.5%).	MS is highly prevalent among patients with established atherosclerotic disease.	70%

Martins, et al., (2021)	Cross-sectional observational study	Humans	Adult patients diagnosed with MS.	MDA, IL-6, TNF-α, SOD, CAT, GPx	Levels of MDA, IL-6, and TNF-α were significantly higher in patients with MS compared to controls.	Patients with MS present increased oxidative stress and systemic inflammation. A compensatory activation of the cholinergic anti-inflammatory pathway may occur in response to a pro-inflammatory state.	80%
Rojas Martínez, et al., (2021)	Cross-sectional observational study	Humans	Mexican adults aged 20 years or older who participated in the ENSANUT surveys in 2006, 2012, and 2018.	N/A	The prevalence of MS was 36.8% in 2006, 35.8% in 2012, and 36.1% in 2018. The most prevalent component was abdominal obesity, mainly among women.	Abdominal obesity is the most prevalent component of MS and has shown an increase, particularly in women.	60%
Silveira Rossi, et al., (2022)	Systematic review	N/A	N/A	N/A	N/A	MS is associated with a chronic low-grade inflammatory state and increased oxidative stress, both contributing to the development and progression of CVD.	60%
Zhao, et al., (2022)	Prospective cohort study	Humans	1,295 NSTEMI patients undergoing PCI.	Troponin T	MS was a predictor of MACE (HR 1.714, p = 0.001). The prognostic value of MS was more pronounced in patients older than 60 years, with LVEF ≤40%, GRACE score >140, multivessel disease, or hsTnT >0.1 ng/ml.	MS is a prognostic factor in patients diagnosed with NSTEMI, especially among those of older age and with higher ischemic risk. A BMI ≥28 kg/m² independently predicted the occurrence of MACE	80%
Costa, et al., (2024)	Retrospective observational study.	Humans	177 patients with chronic total occlusion undergoing PCI.	N/A	Angina was more frequent in people with diabetes (15.2%, p = 0.043). T2DM was not an independent predictor.	T2DM was not associated with a higher overall recurrence of symptoms, but diabetic patients experienced more recurrent angina.	70%

Table3: Studies addressing the association of Metabolic Syndrome with Coronary Vascular Diseases.

ICAM-1 in post-percutaneous coronary intervention (PCI) outcomes.

The spectrum of factors associated with worse outcomes after percutaneous coronary intervention (PCI) is broad, encompassing both metabolic and inflammatory variables. Among these determinants, biomarkers such as ICAM-1 have become increasingly important due to their association with endothelial dysfunction, atherogenesis, and post-PCI complications.

The "other" studies category includes research on microvascular dysfunction, visceral adiposity, and thrombotic risk. Among these, the work of Yu (20) stands out, demonstrating that serum levels of VCAM-1 and ICAM-1 can independently estimate MACE risk in patients with STEMI. ICAM-1 was closely associated with endothelial inflammation and atherosclerotic progression, whereas VCAM-1 showed a robust discriminatory capacity (AUC = 0.852; 95% CI: 0.790–0.914), which was superior to that of ICAM-1 (AUC = 0.805; 95% CI: 0.734–0.875). Both biomarkers elevate significantly in STEMI compared with controls ($p < 0.001$). The cumulative risk of MACE in patients with high VCAM-1 levels was 9.9% in one year, 14.9% in two years, and 22.0% in three years, percentages consistently higher than those in patients with low levels ($p = 0.002$). The authors observed similar results for ICAM-1 ($p = 0.012$). When these biomarkers are integrated with classic clinical factors such as age, diabetes, CRP, and multivessel disease, predictive capacity increases significantly using validated nomograms.

Conversely, the components of metabolic syndrome exerted a significant impact on coronary microvascular function, fostering inflammatory processes and insulin resistance. This phenomenon was associated with an increased risk of hospitalization for heart failure among women undergoing PCI. Within this context, the visceral adiposity index (VAI) emerged as a robust and independent predictor of adverse cardiovascular events in patients with NSTE-ACS and type 2 diabetes. The evidence demonstrates a clear dose–response relationship, consistent across diverse clinical subgroups, as well as a substantial enhancement in the predictive accuracy of traditional prognostic models when VAI is incorporated, thereby reinforcing its role as a key tool for cardiovascular risk stratification [21] (Table 4).

Authors, year of publication	Study Type	Study Model	Study Population	Proteins Measured and Quantification Method	Statistical Data	Relation to the Research Question	PRISMA Quality Rating
Zykov, et al., (2020)	Retrospective observational study.	Humans	Hospitalized patients who underwent emergency PCI for acute myocardial infarction.	N/A	N/A	Women had higher in-hospital mortality following emergency PCI, possibly due to a greater burden of comorbidities and pathophysiological differences.	70%
Uslu, et al., (2020)	Prospective observational study.	Humans	156 patients with STEMI undergoing primary PCI	N/A	Epicardial adipose tissue thickness >5.3 mm predicted thrombus burden (AUC 0.796; OR 2.53, $p < 0.001$).	Epicardial adipose tissue thickness is a predictor of thrombotic burden in STEMI.	80%
Zhao, et al., (2021)	Prospective observational study.	Humans	Patients with NSTEMI-ACS and type 2 diabetes undergoing elective PCI.	VAI	The VAI demonstrated significant predictive ability for MACE.	VAI improves event prediction in patients with NSTEMI-ACS and T2DM.	60%

Lin, et al., (2022)	Retrospective cohort study	Humans	67,534 patients with MI who underwent PCI or CABG.	N/A	Women undergoing PCI had higher hospitalization rates for HF (10.4% vs. 8%, OR 1.32).	Worse outcomes were observed in women after PCI.	80%
Yu, et al., (2022)	Prospective cohort study	Humans	373 patients with STEMI and 50 healthy controls.	VCAM-1 e ICAM-1	VCAM-1 (HR 2.34, p = 0.031) and ICAM-1 (p = 0.012); model AUC: 0.764–0.778.	VCAM-1 and ICAM-1 predict MACE, with ICAM-1 directly linked to endothelial dysfunction and adverse outcomes.	90%
Ma, et al., (2024)	Retrospective cohort study	Humans	Patients with atherosclerotic cardiovascular disease undergoing PCI.	PCSK9	Contrast-associated acute kidney injury (CA-AKI): 5.09% in the evolocumab group vs. 14.16% in the control group (OR 0.502; p = 0.006).	PCSK9 inhibition was associated with a reduction in contrast-induced renal injury.	60%
Jiang, et al. (2025)	Retrospective cohort study.	Humans	2,533 women undergoing PCI.	AIP (log [TG/HDL])	AIP was an independent predictor of MACE in women after PCI.	AIP was an independent predictor of MACE in women after PCI.	70%
Tang, et al., (2025)	Systematic review.	N/A	N/A	AGEs, leptin, adiponectin, TNF-α, IL-6, IL-1β	N/A	The components of MetS exacerbate coronary microvascular dysfunction through inflammation and insulin resistance.	80%

Table4: Studies addressing proteins involved in the occurrence of Metabolic Syndrome and cardiac events.

NGAL, MMP-9, ICAM-1, and PCSK9: Predictors of Atherosclerosis and Angina.

Identifying predictive biomarkers in patients with acute coronary syndrome and stable coronary artery disease is essential for more accurate risk stratification. Among these, NGAL (Neutrophil Gelatinase-Associated Lipocalin) has proven to be a relevant marker. A prospective longitudinal study in patients with stable coronary artery disease treated with percutaneous coronary intervention (PCI) demonstrated that elevated NGAL levels were independently associated with increased all-cause mortality and major adverse cardiovascular events (MACE) [22].

Regarding PCSK9, patients with chronic coronary artery disease exhibited significantly higher serum levels than controls (96.4 ± 33.2 ng/mL vs. 81.8 ± 27.6 ng/mL, $p < 0.05$), and these levels correlated with the severity of coronary artery lesions [23]. The latter suggests that PCSK9 not only regulates LDL cholesterol levels but may also reflect atherosclerotic progression and endothelial dysfunction.

Matrix metalloproteinases, particularly MMP-9, have been associated with atherosclerotic plaque instability and the progression of cardiovascular disease. Studies indicate that elevated MMP-9 levels correlate with a higher risk of adverse cardiovascular events, highlighting its role as a marker of vascular remodeling and extracellular matrix degradation, especially in prehypertension and type 2 diabetes [24].

In a study of obese women, inflammatory markers, C-peptide, IL-10, and alterations in glucose metabolism were evaluated. Levels of sICAM-1, sVCAM-1, E-selectin, CCL2, and C-reactive protein (CRP) were significantly higher in obese women compared with controls ($p < 0.05$). In the subgroup with newly diagnosed type 2 diabetes, C-peptide levels correlated positively with E-selectin, CCL2, and triglycerides, and inversely with IL-10 ($p < 0.05$). Furthermore, IL-10 showed negative correlations with E-selectin, CCL2, C-peptide, and HOMA-IR, indicating that a more intense inflammatory state and greater insulin resistance are associated with reduced anti-inflammatory capacity. These findings suggest that obesity, particularly when accompanied by type 2 diabetes, exacerbates endothelial activation and systemic inflammation, underscoring the relevance of ICAM-1 as a marker of endothelial dysfunction and cardiovascular risk in this population [25].

Taken together, these biomarkers constitute key tools for evaluating cardiovascular risk in patients with angina and stable coronary artery disease (Figure 2). Their measurement may guide risk stratification, identify patients at higher risk of adverse events, and inform the implementation of personalized therapeutic strategies to improve clinical outcomes (Table 5).

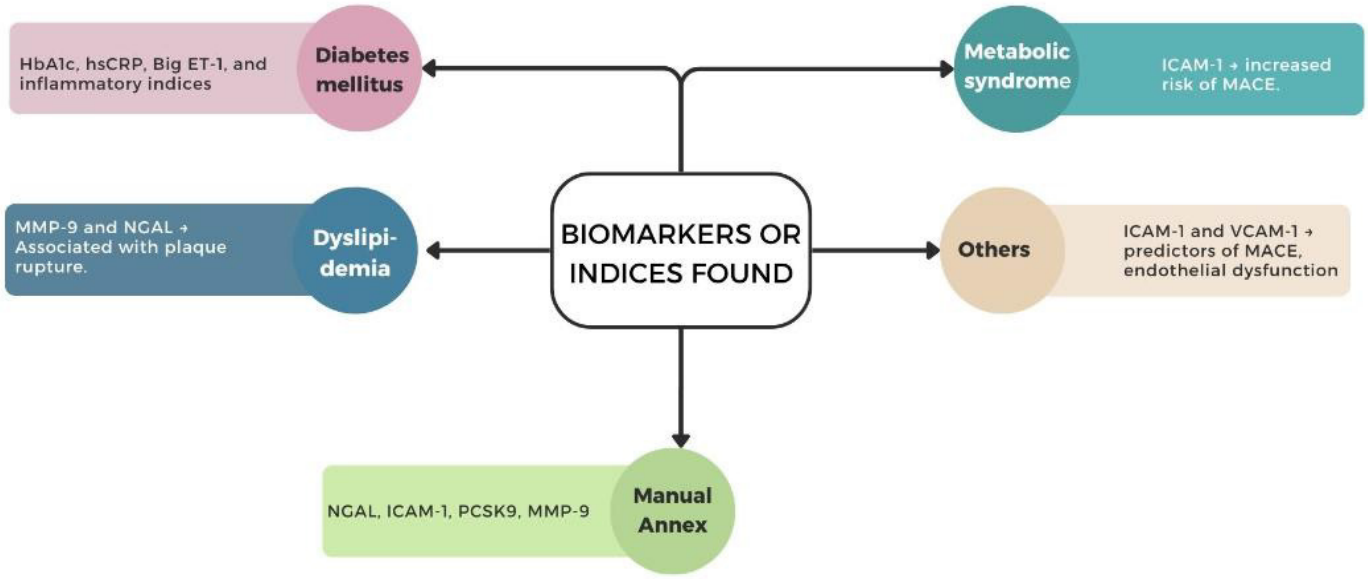

Figure2: Classification of the included studies into five main categories (diabetes mellitus, dyslipidemia, metabolic syndrome, others, and manual annex) and distribution of the biomarkers of interest (NGAL, MMP-9, ICAM-1, and PCSK9).

Authors, year of publication	Study Type	Study Model	Study Population	Proteins Measured and Quantification Method	Statistical Data	Relation to the Research Question	PRISMA Quality Rating
Tadzic et al., (2013)	Prospective clinical study	Humans	24 hypertensive subjects	sICAM-1, VCAM-1, E-selectin,	Post-treatment reduction: sICAM-1 decreased significantly after 8 weeks ($p \leq 0.001$).	Amlodipine significantly reduced blood pressure and decreased sICAM-1, reflecting reduced endothelial activation.	80%

Janowska et al., (2016)	Cross-sectional observational study	Humans	61 obese women and 20 normal-weight controls	sICAM 1, sVCAM 1, E selectin, CCL2 (MCP 1)	sICAM-1 levels were higher in T2DM, correlating with glucose and HDL ($p < 0.05$).	Obese women with type 2 diabetes exhibited significantly elevated sICAM-1, reflecting endothelial dysfunction.	80%
Kostov et al., (2016)	Analytical cross-sectional observational study	Humans		Endothelin 1 (ET 1), MMP 2, and MMP 9	MMP-2 and MMP-9 levels increased early in Prehypertension: 49.6 ($p < 0.0001$ vs. N) Hypertension: 35.6 ($p < 0.0002$ vs. control ; $p < 0.002$ vs. PHTN).	MMP-2 and MMP-9 rise early in prehypertension, indicating early vascular remodeling and extracellular matrix degradation.	80%
Wang et al., (2016)	Analytical observational case–control study	Humans	126 patients with coronary heart disease (stenosis ≥50%) and 70 controls	PCSK9	Higher plasma PCSK9 in CHD patients (96.4 vs. 81.8 ng/mL, $p < 0.05$).	PCSK9 may serve as a biomarker of coronary disease severity, implicated in endothelial dysfunction and indirectly in metabolic syndrome.	80%
Wang, et al., (2016)	Experimental study	Mice	120 male $ApoE^{-/-}$ mice	Adiponectin, MMP 9	Treatment with adiponectin reduced serum MMP-9 and slowed plaque progression ($p < 0.05$).	Exogenous adiponectin significantly attenuates atherosclerotic plaque development in $ApoE^{-/-}$ mice, reducing MMP-9 levels and modulating vascular matrix degradation and plaque stability.	90%
Xu et al., (2018)	Cross-sectional observational study	Humans	1,179 individuals.	OCN, FGF-23, and NGAL by chemiluminescence immunoassay	FGF-23 and NGAL showed positive correlations with metabolic indices ($p < 0.05$)	Higher serum NGAL levels imply a ~29% increased risk of visceral obesity.	80%
Litvinova et al. (2019)	Cross-sectional observational study	Humans	88 obese patients; 20 healthy controls	ICAM-1, VCAM-1, IL-6, TNF-α, PCR	ICAM-1 correlated with glucose in obese patients with and without T2DM ($r \approx 0.45$, $p < 0.05$).	Obesity and T2DM were associated with significantly increased plasma ICAM-1 compared with controls and obese non-diabetics.	80%

Lin, et al, (2025)	Prospective longitudinal cohort study	Humans	2238 pacientes	NGAL, NT-proBNP, CRP.	The addition of NGAL improved the predictive capacity of models for heart failure (69.9% accuracy), total cardiovascular events (65.5%), revascularization (61.2%), and new dialysis (73.4%).	Higher serum NGAL levels were associated with a greater risk of MACE, including CV events, CV mortality, and target vessel revascularization.	80%
Mayyas (2025)	Cross-sectional study	Humans	373 patients	Lipocalin-2	Significant associations with PCI, CAD, LDL, diabetes, HbA1c, and coronary stenosis ($p < 0.05$).	NGAL was a predictor of PCI revascularization and may reflect atherosclerotic plaque instability, given its association with infarction progression and MMP-9 expression.	80%

Table5: Studies addressing the association between proteins involved in metabolic alterations.

Discussion

The components of metabolic syndrome, such as abdominal obesity, dyslipidemia, hypertension, insulin resistance, and chronic proinflammatory status, create an atherogenic environment [18,26]. These factors directly contribute to endothelial damage and the progression of cardiovascular disease. Several proteins have been identified in this process, notably PCSK9, which binds to LDL receptors, increasing the availability of lipid particles and promoting atherosclerotic plaque formation (27,28); ICAM-1, which facilitates leukocyte adhesion and plaque inflammation [16]; and the NGAL/MMP-9 complex, which degrades the extracellular matrix and favors rupture of unstable plaques [15].

Given their involvement in this process, we considered it relevant to conduct a systematic review to determine whether studies exist that report alterations in the serum concentrations of these proteins in patients with MS undergoing coronary intervention. To provide a comprehensive overview, we first summarize the scope of the studies reviewed before discussing each protein in detail.

In the present epistemic meta-analysis, we reviewed 53 articles. Of these, 58.5% addressed type 2 diabetes mellitus, 18.9% dyslipidemia, 15.1% metabolic syndrome, 13.2% systemic arterial hypertension, and 11.3% obesity. Among the articles focusing on type 2 diabetes, 65% addressed adverse vascular events after PCI, 20% mortality, and 5% endothelial dysfunction or neointimal hyperplasia. Within this group, studies highlighted the association between diabetes and sustained increases in ICAM-1 and PCSK9, contributing to a chronic inflammatory profile and increased vascular stiffness post-intervention [25].

Regarding the articles addressing dyslipidemia, 37.5% focused on plaque vulnerability, 25% on clinical complications or neo-atherosclerosis, and 12.5% reported an association with poor prognosis. These studies underscore the role of PCSK9 as a key modulator of lipid metabolism and its direct involvement in post-PCI neo-atherosclerosis. In turn, articles on metabolic syndrome revealed that 37.5% focused on endothelial dysfunction and 12.5% on mortality and post-interventional complications. In this category, studies found an association between MS and increased serum levels of NGAL and MMP-9, markers of plaque fragility and higher rates of restenosis [15,29].

PCSK9: Beyond Lipid Metabolism, an Inflammatory Modulator.

PCSK9 was addressed in 3.77% of the articles and is associated with the severity of coronary disease. Although initially identified for its role in cholesterol metabolism through LDL receptor degradation, PCSK9 also exerts inflammatory functions in the vascular wall, promoting endothelial cell apoptosis and proatherogenic processes independent of cholesterol [23]. Furthermore, Wang reported significantly higher PCSK9 levels in patients with MS and coronary artery disease [23]. Treatment with PCSK9 inhibitors (PCSK9i) for six months demonstrated to improve endothelial function and peripheral microcirculation, as reflected by a significant increase in flow-mediated dilation (FMD), which supports the role of PCSK9 not only in lipid imbalance but also in chronic

vascular inflammation, reactive oxygen species generation, and endothelial apoptosis, thereby exacerbating vascular dysfunction [30].

ICAM-1: An Early Marker of Endothelial Activation.

ICAM-1 was discussed in 9.4% of all articles, all of which emphasized elevated serum concentrations in MS patients, associated with significant adverse cardiovascular events (MACE), endothelial dysfunction, obesity, diabetes, and hypertension. ICAM-1 is a surface protein expressed on activated endothelial cells that participates in leukocyte recruitment to inflamed endothelium. Moreover, studies have documented its elevation in patients with MS comorbidities [27].

Litvinova et al. (2019) demonstrated that plasma ICAM-1 levels, measured by ELISA, were elevated in patients with visceral obesity and hyperglycemia [31]. This condition favors advanced protein glycation and the activation of inflammatory pathways, which in turn upregulate its expression. Increased circulating ICAM-1 also correlated positively with CRP, leptin, TNF-α, and IL-6, underscoring the role of proinflammatory mediators in endothelial dysfunction. Other authors reported an association between increased ICAM-1 and hypertension, showing decreased ICAM-1 levels following blood pressure reduction with amlodipine treatment [32]. According to Yu et al. (2022) [33], ICAM-1 serves as an early indicator of endothelial activation, reflecting a chronic state of vascular inflammatory stress that precedes atherosclerotic plaque formation by regulating the transcription of mineralocorticoid receptors (MR). Therefore, increased ICAM-1 levels may be considered a risk factor for adverse cardiovascular events by promoting fibrosis, vascular hypertrophy, macrophage infiltration, and reactive oxygen species production.

NGAL: A Link Between Visceral Obesity, Inflammation, and Atherosclerotic Progression.

NGAL was addressed in 5.6% of the 53 reviewed articles, highlighting its role in glucose homeostasis by influencing glucose tolerance, insulin sensitivity, and insulin secretion, as well as its close association with visceral obesity and type 2 diabetes mellitus [34]. Its prognostic utility has also been demonstrated in cardiac arrest survivors, where elevated plasma NGAL levels on day 3 post-event were associated with worse long-term outcomes [35].

In a study by Mayyas [36] analyzing NGAL concentrations via ELISA in patients with coronary artery disease undergoing PCI, plasma NGAL levels were higher compared to controls and correlated with the number of affected vessels, reflecting disease severity and plaque instability, thereby supporting its role as a prognostic biomarker in CAD. From a pathophysiological perspective, NGAL is implicated in the progression of atherosclerosis by promoting endothelial dysfunction, inflammation, and extracellular matrix degradation through its interaction with MMP-9, which leads to plaque instability. Indeed, patients with acute myocardial infarction present significantly elevated NGAL levels compared with those with stable CAD [37]. Elevated NGAL concentrations predict both all-cause mortality and MACE, particularly in STEMI patients treated with PCI [38]. In a recent article by Lin (2025) [39], NGAL was identified as a predictor of complications following PCI, particularly congestive heart failure, MACE, total cardiovascular events, repeat revascularization, and new-onset hemodialysis in stable CAD patients.

MMP-9: The Architect of Plaque Destabilization.

MMP-9 is an enzyme involved in collagen degradation and the breakdown of other extracellular matrix components. Ninety-four percent of the reviewed articles mentioned it, mainly as a marker of diabetes, elevated during plaque rupture, vascular remodeling, matrix degradation, and plaque instability [37].

According to Wang et al. (2016) [40] MMP-9 is overexpressed in advanced atherosclerotic plaques, particularly in macrophage-rich areas, suggesting a critical role in plaque rupture by degrading extracellular matrix components such as collagen, elastin, and proteoglycans, thereby making it a pivotal modulator of plaque stability. In murine models, such as Ldlr−/− Apob100/100, MMP-9 was significantly upregulated in advanced lesions. However, adiponectin treatment reduced its expression, along with that of inflammatory markers, indicating a potential anti-inflammatory therapeutic pathway. Moreover, in patients with acute coronary syndrome (ACS), elevated MMP-9 levels are associated with greater myocardial injury (reflected by higher CK-MB and leukocyte counts), more frequent STEMI presentations, and genetic polymorphisms that increase its expression [37].

The Pathophysiological Process: From Metabolic Stress to Plaque Rupture.

The pathophysiology of ACS is based on the progression of atherosclerosis, a chronic inflammatory process of the vascular intima closely linked to MS, which encompasses abdominal obesity, insulin resistance, hypertension, dyslipidemia, and impaired glucose metabolism [41]. A key mediator in this progression is PCSK9, a regulator of LDL cholesterol metabolism. When overexpressed, PCSK9 induces endothelial injury, apoptosis, and LDL-C accumulation, thereby accelerating vascular damage. In contrast, its inhibition reduces circulating LDL-C and attenuates the progression of CAD [40].

Vascular injury initiation and progression involve multiple cellular and molecular mechanisms, including subendothelial lipid accumulation, leukocyte recruitment, and local smooth muscle cell proliferation [27,41].

Macrophage infiltration of the intima and transformation into foam cells via phagocytosis of modified LDL develop plaques with a lipid core and a fibrous cap. The latter, when thinned and weakened, becomes a critical rupture site [42]; it is also exacerbated by elevated triglycerides and small,

dense LDL-C particles, which evade clearance by traditional receptors, further fueling inflammation through intracellular accumulation in macrophages [41,42].

In this proinflammatory and dyslipidemic milieu, matrix metalloproteinases (MMP-2 and MMP-9) play a central role. Their activity is markedly increased in patients with metabolic dysfunction, contributing to collagen degradation in the fibrous cap and weakening the plaque, thereby favoring rupture and thrombus formation [43]. Specifically, MMP-9, secreted by endothelial cells, macrophages, and myofibroblasts, enhances its destabilizing effect when bound to NGAL, a glycoprotein expressed by neutrophils, smooth muscle cells, and endothelial cells in atherosclerotic plaques. This interaction increases MMP-9 activity and contributes to plaque instability, even without inducing direct rupture [37].

Finally, endothelial dysfunction, exacerbated by metabolic factors and procedures such as PCI, manifests clinically as reduced nitric oxide (NO) release and increased endothelin-1 (ET-1) levels, which raise microvascular resistance and compromise myocardial perfusion, thereby completing the pathogenic cycle leading to ACS [44] (Figure 3).

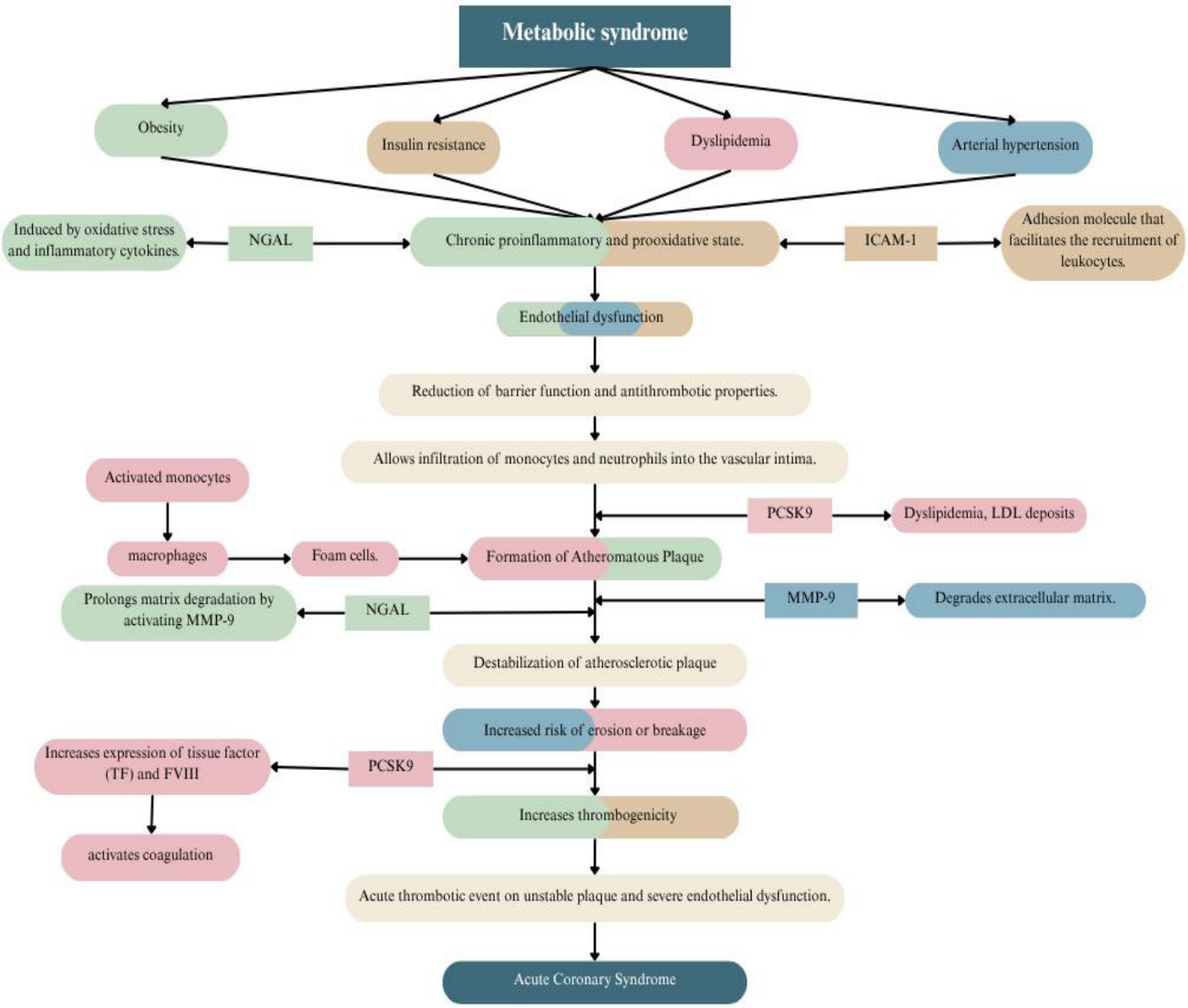

Figure3: Schematic representation of how metabolic síndrome promotes a proinflammatory and pro-oxidative state that triggers endothelial dysfunction. Four key biomarkers are highlighted: NGAL (linked to obesity; green), ICAM-1 (associated with insulin resistance; brown), PCSK9 (related to dyslipidemia; pink), and MMP-9 (linked to hypertension; blue).

Conclusions

The alterations explain why patients with MS exhibit poorer outcomes following PCI. Post-PCI complications include increased risks of restenosis, stent thrombosis, and MACE, all of which are associated with persistent systemic inflammation, maladaptive vascular remodeling, and sustained activation of biomarkers such as NGAL, MMP-9, and ICAM-1. Several studies have demonstrated that serum levels of these molecules remain elevated after PCI, linking them to worse clinical outcomes and increased risk of recurrent adverse events.

Finally, within the "others" group, which includes mixed-approach studies, 62.5% addressed adverse events or poor outcomes post-PCI, 25% addressed endothelial dysfunction, and 12.5% addressed mortality. This evidence reinforces the notion that, regardless of the specific comorbidity, biomarkers of endothelial damage, such as ICAM-1, PCSK9, NGAL, and MMP-9, remain elevated in MS and CAD and that their persistence after intervention is associated with a poorer prognosis.

The reviewed evidence highlights ICAM-1, PCSK9, NGAL, and MMP-9 as key proteins in the pathophysiology of MS and its progression to CAD. Their elevated serum concentrations in patients with metabolic comorbidities, commonly measured by ELISA, reflect chronic inflammation and endothelial dysfunction. Moreover, their increase following PCI is linked to adverse clinical outcomes.

In this systematic review, only the study by Mayyas(36) specifically addressed our research question, although it focused exclusively on NGAL. This gap in the current literature represents a critical inflection point, underscoring the need to develop new research protocols investigating these proteins as emerging biomarkers. The latter presents a valuable opportunity for their future application in detection, prognosis, and targeted therapy in patients with MS undergoing coronary intervention.

Declarations

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Data availability

Research data is available upon request. To request the data, please contact the corresponding author.

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