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Review article

EMERGING BIOMARKERS AT THE CROSSROADS OF CARDIAC, RENAL, AND HEPATIC DYSFUNCTION: A NEW ERA IN MULTIORGAN RISK STRATIFICATION

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Abstract

The cardio-hepato-renal axis represents a complex interplay of organ systems whose dysfunction contributes to high morbidity and mortality in chronic disease. Traditional biomarkers such as natriuretic peptides, creatinine, and liver transaminases provide limited insight into the early and overlapping pathophysiological changes within this tri-organ network. Emerging biomarkers - including ischemia-modified albumin (IMA), soluble ST2 (sST2), galectin-3, thrombin–antithrombin complex (TAT), neutrophil gelatinase-associated lipocalin (NGAL), hyaluronic acid (HA), and matrix metalloproteinase-9 (MMP-9) - offer novel perspectives by reflecting oxidative stress, myocardial fibrosis, neurohumoral activation, coagulation activity, renal tubular injury, extracellular matrix remodeling, and systemic inflammation. This review synthesizes current evidence on the mechanistic relevance, diagnostic performance, and prognostic value of these biomarkers across diverse clinical contexts such as acute coronary syndromes, heart failure, atrial fibrillation, sepsis, and cardio-hepato-renal syndrome. We highlight their potential integration into multimarker panels and precision medicine strategies, emphasizing their role in early detection, risk stratification, and therapeutic monitoring. By shifting from isolated organ assessment to systemic biomarker profiling, these tools may transform clinical practice, enabling more holistic management of multiorgan dysfunction and improving patient outcomes.

Keywords: oxidative stress, extracellular matrix remodeling, fibrosis, neurohumoral activation, cardiac remodeling, acute kidney injury, hepatic fibrosis, cardio-hepato-renal dysfunction

Introduction

The intricate interplay between the heart, kidneys, and liver forms a dynamic physiological network essential for maintaining systemic homeostasis. In the setting of chronic disease, however, this tri-organ axis becomes a conduit for progressive dysfunction, where

impairment in one organ often precipitates or exacerbates pathology in the others. This phenomenon, increasingly recognized as the cardio-hepato-renal syndrome (CHRS), represents a complex clinical entity with high morbidity and mortality, particularly in patients with advanced heart failure, chronic kidney disease (CKD), and hepatic congestion. Despite its clinical relevance, CHRS remains underdiagnosed and poorly characterized, largely due to the lack of sensitive and specific biomarkers capable of capturing the early and overlapping pathophysiological changes across these organ systems [1-10].

Traditional biomarkers such as NT-proBNP, serum creatinine, and liver transaminases offer limited insight into the nuanced and often subclinical interactions within the cardio-hepato-renal axis. These conventional markers are often reactive rather than predictive, rising only after significant organ damage has occurred. In contrast, a new generation of biomarkers is emerging-molecules that reflect early tubular injury, myocardial fibrosis, hepatic congestion, systemic inflammation, and extracellular matrix remodeling. These include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), galectin-3, soluble ST2, hyaluronic acid, and matrix metalloproteinases, among others. Their integration into clinical practice holds the potential to transform the diagnostic and prognostic landscape of multiorgan syndromes [1-10].

This review aims to synthesize current evidence on novel biomarkers that illuminate the pathophysiological crosstalk between the heart, liver, and kidneys. We explore their mechanistic relevance, diagnostic performance, and prognostic value in various clinical contexts, including acute decompensated heart failure, cardiorenal syndrome, and hepatic congestion. Furthermore, we discuss how these biomarkers can be incorporated into multimodal risk stratification tools and personalized care pathways, aligning with the goals of precision medicine and integrated chronic disease management.

By shifting the focus from isolated organ assessment to systemic biomarker profiling, clinicians and researchers can better anticipate clinical deterioration, tailor interventions, and ultimately improve outcomes in patients with cardio-hepato-renal dysfunction. As the field moves toward a more holistic understanding of multiorgan disease, these emerging biomarkers offer a promising bridge between molecular insight and clinical action.

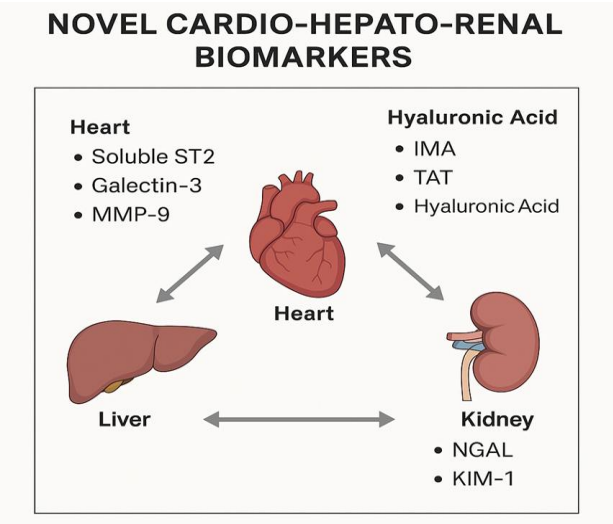

Fig. 1. Central illustration-Novel Cardio-Hepato-Renal Biomarkers
(AI generated image by the authors)

Ischemia-Modified Albumin (IMA) in Myocardial Ischemia

Myocardial ischemia is a central pathophysiological process defining ischemic heart disease, leading to metabolic derangements and oxidative stress, characterized by excessive reactive oxygen species (ROS) release, contributing to cellular injury and seting the stage for necrosis if left untreated. Traditional biomarkers such as cardiac troponins and CK-MB have transformed the diagnosis of myocardial infarction. However, they primarily reflect established myocardial injury rather than the earliest ischemic changes. Against this backdrop, Ischemia-Modified Albumin (IMA) has emerged as a sensitive biomarker capable of detecting ischemia within minutes of onset [1].

Mechanism of formation of IMA is as follows: hypoxia and acidosis during ischemia promote ROS generation; ROS induce structural changes in the N-terminal region of albumin, leading to reduction of albumin's cobalt-binding affinity, and production of the altered form known as IMA. IMA levels rise rapidly in plasma, often within minutes of ischemia, and linking IMA directly to oxidative stress, positioning it as a dynamic marker of ischemic injury[2] .

Additionally, oxidative stress resulting in increased ROS such as superoxide anions, hydrogen peroxide, and hydroxyl radicals damage proteins, lipids, and nucleic acids. Albumin, due to its antioxidant properties, is among the first proteins to be modified. The formation of IMA reflects the extent of oxidative modification and serves as a surrogate marker of oxidative stress[3] . This property distinguishes IMA from conventional biomarkers, which primarily indicate necrosis rather than the oxidative processes preceding it.

Clinical relevance in myocardial ischemia is demonstrated in early diagnosis. IMA levels increase within 6–10 minutes of ischemia, peak at approximately 30 minutes, and remain elevated for up to 6 hours. This rapid and transient profile makes IMA especially valuable in ACS, where early recognition is paramount[2]. The Albumin Cobalt Binding (ACB) test measures the reduced cobalt-binding capacity of albumin. A positive result indicates ongoing ischemia even in the absence of necrosis[4,5]. Interpreted alongside other biomarkers of myocardial injury (troponins, CK-MB, etc.), diagnostic sensitivity improves significantly, enhancing its utility in ruling out myocardial infarction in the acute care environment[2,5]. Limitations and considerations at the present are non-specificity, short half-life, and analytical variability[4]. Future directions are in developing high-sensitivity assays, integration into emergency and outpatient settings (point-of-care testing), and combination of IMA with inflammatory and oxidative stress markers by creating multimarker panels [1,3].

Ischemia-modified albumin represents a valuable biomarker for the early detection of myocardial ischemia, reflecting oxidative stress and ischemic injury within minutes of onset. While its lack of specificity limits its standalone use, its role as an adjunct in multimarker strategies is increasingly recognized. Continued research into assay refinement, point-of-care applications, and multimarker integration will determine how best to harness IMA in clinical practice.

Soluble ST2 (sST2) as a Prognostic Biomarker in Heart Failure and Cardiovascular Disease

Heart failure (HF) remains a major global health challenge, with high rates of morbidity, mortality, and hospital readmissions. Accurate risk stratification and monitoring of disease progression are essential for optimizing therapeutic strategies. Traditional biomarkers such as natriuretic peptides (NPs) provide valuable diagnostic and prognostic information, but they have limitations, particularly in differentiating between heart failure phenotypes and predicting long-term outcomes. Soluble ST2 (sST2), a member of the interleukin-1 receptor family, has emerged as a robust biomarker reflecting myocardial stress, inflammation, and fibrosis. Elevated sST2 levels are associated with adverse cardiac remodeling and poor prognosis in both heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction

(HFpEF). Its unique pathophysiological role and prognostic strength make sST2 a promising candidate for incorporation into clinical practice[6] .

Clinical significance of sST2 is in the settings of acute and chronic heart failure, as well as in coronary artery disease (CAD). In heart failure, elevated sST2 levels independently predict mortality and hospitalization, and unlike NPs, its levels are not influenced by age, body mass index, atrial fibrillation, or gender, making it a stable and reliable biomarker[7]. In CAD, sST2 reflects plaque burden and inflammatory activity and predicts no-reflow events after percutaneous coronary interventions. Elevated levels are associated with worse outcomes in patients with myocardial infarction[8]. The PRIDE study demonstrated that sST2 levels independently predicted 4-year mortality, even after adjusting for clinical, biochemical, and echocardiographic risk markers[9] , demonstrating its prognostic value. Elevated sST2 levels are strongly associated with sudden cardiac death in patients with mild to moderate systolic HF. Thus, sST2 is a powerful biomarker for risk stratification, prognosis, and therapeutic guidance in cardiovascular disease.

Soluble ST2 (suppression of tumorigenicity 2) belongs to the interleukin-1 receptor family and exists in two isoforms: ST2L (transmembrane form), and sST2 (soluble form). The IL-33/ST2L signalling pathway plays a cardioprotective role by reducing myocardial fibrosis, limiting cardiomyocyte hypertrophy and apoptosis, and improving myocardial function. During cardiac stress or injury, cardiomyocytes and fibroblasts upregulate IL-33/ST2L signalling. However, elevated sST2 acts as a decoy receptor, binding IL-33 and preventing its interaction with ST2L. This disrupts the cardioprotective pathway, leading to increased myocardial fibrosis, adverse remodelling and progression of heart failure[10] . The main sources of sST2 are cardiomyocytes, fibroblasts, and endothelial cells under stress or injury. High circulating levels of sST2 therefore reflect myocardial strain, inflammation, and fibrosis, correlating with disease severity and prognosis.

sST2 has multiple clinical applications, specifically in risk stratification in heart failure - elevated sST2 levels are associated with a twofold increase in mortality risk, independent of NPs and other clinical parameters[11], and at the same time demonstrating strong reclassification power, particularly in patients with low NP levels. Incorporated into risk scores such as the Seattle Heart Failure Model, sST2 enhances predictive accuracy for mortality and hospitalization. Also, sST2 can serve for therapeutic monitoring (response to therapy), and disease progression, and for guiding therapeutic treatment intensity, particularly in advanced HF management. In patients with CAD and myocardial infarction, sST2 predicts adverse outcomes, including sudden cardiac death and no-reflow events post-intervention [18] .

Soluble ST2 (sST2) is a novel and powerful biomarker in cardiovascular disease, particularly in heart failure. By reflecting myocardial stress, inflammation, and fibrosis, sST2 provides prognostic information beyond traditional biomarkers such as natriuretic peptides. Its stability across demographic and clinical variables, combined with its strong predictive value for mortality and hospitalization, makes sST2 a valuable tool for risk stratification, therapeutic monitoring, and guiding clinical management. Future research should focus on integrating sST2 into multimarker panels and exploring its role in personalized medicine approaches for heart failure and CAD.

Galectin-3 as a Marker of Neurohumoral Activation and Fibrosis in Heart Failure

Galectin-3 (Gal-3) is another powerful biomarker in heart failure patients. Gal-3 has attracted significant attention due to its role in inflammation, fibrosis, and ventricular remodelling - hallmarks of HF pathophysiology.

Galectin-3 is a 30-kDa β-galactoside-binding lectin, encoded by the *LGALS3* gene, and expressed predominantly in activated macrophages, epithelial cells, and immune cells. It is

secreted via a non-classical pathway and functions both intracellularly and extracellularly, contributing to cell adhesion, proliferation, apoptosis, and immune responses [12,13] .

Galectin-3 belongs to the chimera-type galectin family, consisting of a carbohydrate-recognition domain (CRD) and an N-terminal domain that enables oligomerization. This structural feature allows Gal-3 to cross-link glycoproteins on the cell surface and extracellular matrix. Upon injury or stress, Gal-3 is secreted by macrophages and binds to glycoproteins such as integrins and laminins, initiating pro-inflammatory and pro-fibrotic signalling cascades [13]. In the failing myocardium, Gal-3 is upregulated and activates cardiac fibroblasts, promoting their transformation into myofibroblasts-cells responsible for collagen deposition and fibrosis [14]. These processes contribute to myocardial stiffening, adverse remodelling, and impaired cardiac function. Importantly, Gal-3 activation is triggered and sustained by neurohumoral signals, particularly angiotensin II and aldosterone, linking it directly to the renin-angiotensin-aldosterone system (RAAS). This positions Gal-3 as a biomarker that overlaps with, but also extends beyond, classical neurohumoral markers such as natriuretic peptides, by capturing aspects of tissue inflammation and extracellular matrix remodelling [12,13].

Detection and Clinical Utility

Galectin-3 can be measured in plasma or serum using ELISA-based immunoassays. Clinical studies have shown that levels above 17.8 ng/mL are associated with increased mortality and hospitalization in HF patients [15]. Unlike natriuretic peptides (BNP, NT-proBNP), which reflect cardiac stretch and volume overload, Gal-3 signals fibrosis and chronic inflammation -key drivers of HF progression [13] . This complementary biological axis makes Gal-3 particularly valuable for risk stratification in chronic HF, early detection of structural remodelling before overt functional decline, and prognostic assessment across both HFrEF and HFpEF subtypes.

Gal-3 also serves as an indirect measure of neurohumoral activation. In HF, chronic stimulation of the sympathetic nervous system and RAAS promotes macrophage infiltration and cytokine release. This inflammatory milieu upregulates Gal-3, which enhances fibrotic signalling through TGF-β pathways and further stimulates neurohumoral mediators, creating a vicious cycle of cardiac remodelling and dysfunction [14]. Recent studies highlight the value of Gal-3 in multimarker strategies. For example, when combined with NT-proBNP, Gal-3 improves prognostic accuracy for adverse outcomes in HF patients [15]. Elevated Gal-3 levels are also predictive of progression from asymptomatic diastolic dysfunction to overt HF, making it a candidate for early intervention monitoring.

Consequently, clinical significance and application is in prognosis of chronic HF patients, risk stratification and therapeutic guidance. In the context of multimarker utility it provides additive prognostic value when used alongside natriuretic peptides, reflecting complementary biological pathways.

Galectin-3 is a pivotal biomarker that bridges the gap between inflammation, fibrosis, and neurohumoral activation in heart failure. Its role extends beyond traditional hemodynamic markers, offering insights into the structural and cellular changes underlying cardiac dysfunction. Although not yet universally adopted in clinical guidelines, incorporation of Gal-3 into HF assessment models holds promise for more personalized and biologically informed management strategies.

Multimarker strategy

When viewed together, **Ischemia-Modified Albumin (IMA), soluble ST2 (sST2), and Galectin-3 (Gal-3)** illustrate how modern biomarkers capture different dimensions of cardiovascular disease, complementing one another in both diagnosis and prognosis.

IMA reflects **the earliest biochemical changes of ischemia**, rising within minutes as oxidative stress alters albumin's cobalt-binding capacity. sST2, in contrast, is **a prognostic marker of myocardial stress, inflammation, and fibrosis**. By acting as a decoy receptor for IL-33, it disrupts cardioprotective signalling and promotes adverse remodelling. Unlike natriuretic peptides, sST2 levels are unaffected by age, gender, BMI, or atrial fibrillation, giving it stability across diverse patient groups. Galectin-3 highlights **the fibrotic and inflammatory axis of heart failure**, linking neurohumoral activation with structural remodelling. Gal-3 is particularly valuable in identifying patients at risk of progression and in multimarker strategies alongside NT-proBNP.

Thrombin-Antithrombin Complex (TAT) as a Biomarker of Coagulation Activation

The thrombin–antithrombin (TAT) complex is a sensitive biomarker that reflects activation of the coagulation cascade and ongoing thrombin generation. Formed when thrombin binds to antithrombin, TAT serves as a real-time indicator of hypercoagulability and endothelial dysfunction. Its measurement has gained importance in the diagnosis and management of thrombotic and inflammatory disorders, including atrial fibrillation, venous thromboembolism, disseminated intravascular coagulation (DIC), sepsis, and malignancy [16] . The clinical utility of TAT lies in its ability to detect coagulation activation before overt thrombosis occurs. In sepsis and DIC, elevated TAT levels correlate with systemic coagulation activation, severity of DIC, and organ dysfunction, making it a valuable prognostic marker in critically ill patients [16]. In oncology, malignancies are associated with increased thrombin generation, and elevated TAT levels indicate a hypercoagulable state and may be linked to tumour progression and metastatic risk [17] . In cardiovascular diseases such as acute coronary syndromes and venous thromboembolism, TAT levels reflect ongoing thrombin generation and help stratify thrombotic risk [18] .

Thrombin is a central enzyme in the coagulation cascade, responsible for converting fibrinogen to fibrin, activating platelets, and amplifying coagulation through feedback loops. To prevent uncontrolled clot propagation, thrombin is rapidly neutralized by antithrombin (AT), a serine protease inhibitor. This interaction forms the TAT complex, which circulates in plasma and reflects real-time thrombin activity [19] . In pathological states such as sepsis, cancer, and DIC, thrombin generation becomes excessive, overwhelming natural anticoagulant pathways. Inflammatory cytokines, tissue factor expression, and endothelial damage contribute to this hypercoagulable environment, resulting in elevated TAT levels [20] .

The TAT complex has diverse clinical applications in diagnosis for early detection of hypercoagulable states and DIC, and identification of coagulation activation before clinical thrombosis. In purposes of monitoring, serial TAT measurements in intensive care settings help track coagulation status in patients with sepsis or trauma. In therapeutic treatment monitoring TAT serves as a marker for anticoagulant therapy effectiveness [19] .

The thrombin–antithrombin complex is a sensitive and clinically relevant biomarker of thrombin generation. By reflecting real-time coagulation activity, TAT provides diagnostic, prognostic, and therapeutic insights across a wide range of conditions, including sepsis, cancer, cardiovascular disease, and DIC. Its incorporation into multimarker strategies may further enhance risk stratification and patient management in hypercoagulable states.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) as an Early Biomarker of Acute Kidney Injury

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a 25-kDa glycoprotein belonging to the lipocalin family. It has emerged as one of the earliest and most sensitive biomarkers of acute kidney injury (AKI), particularly in the context of heart failure, sepsis, and

post-cardiac surgery. NGAL levels rise rapidly in both serum and urine within hours of tubular injury, enabling timely diagnosis and intervention before traditional markers such as serum creatinine become elevated [21]. Early identification of AKI is crucial, as renal dysfunction can progress quickly and lead to adverse outcomes.

In clinical settings, NGAL is detectable within 2-4 hours of renal tubular damage, much earlier than serum creatinine, which may take 24-48 hours to rise [22]. NGAL has prognostic role, with elevated levels correlating with the severity and prognosis of AKI [23]. In risk stratification, NGAL provides incremental prognostic information beyond traditional renal markers, supporting its role in early detection and management strategies [23].

Pathophysiology of NGAL: under physiological conditions it is produced in small amount, however, it is markedly upregulated during AKI. NGAL is synthesized and secreted by injured renal tubular epithelial cells, especially in the distal nephron segments, in response to ischemic, toxic, or inflammatory insults [24] . Due to cardio-renal link, increased production is observed in heart failure, reduced cardiac output and venous congestion, all resulting in renal hypoperfusion and tubular stress, and triggering NGAL release. NGAL can also have systemic origin released by activated neutrophils during systemic inflammation, contributing to its elevation in sepsis and multiorgan failure [25] . Its function is to act as an iron-scavenging protein by binding siderophores, limiting bacterial growth and reducing free iron-mediated oxidative stress, and promoting tubular epithelial cell proliferation and repair, explaining its early rise in AKI as part of the regenerative response. Thus, NGAL reflects both local kidney injury and systemic inflammatory processes, making it a unique biomarker that integrates renal and systemic pathophysiology [24,25].

Clinical application of NGAL and its testing has demonstrated utility across multiple clinical scenarios: cardiorenal syndrome, post-cardiac surgery, acute coronary syndromes, sepsis, and in the settings of critical care and emergencies [22,26].

NGAL is a powerful and early biomarker of AKI, rising within hours of tubular injury and providing diagnostic and prognostic information well before traditional markers. Its dual renal and systemic origin allows it to capture both local kidney damage and systemic inflammation, making it particularly valuable in cardiorenal syndrome, sepsis, and perioperative care. As point-of-care testing becomes more widely available, NGAL is poised to play an increasingly central role in the early detection and management of AKI.

Hyaluronic Acid (HA) as a Marker for Cardio-Hepato-Renal Dysfunction

Hyaluronic acid (HA) is a high-molecular-weight glycosaminoglycan found in the extracellular matrix (ECM) of connective tissues, skin, and synovial fluid. It plays a critical role in tissue hydration, elasticity, and repair. In recent years, HA has gained attention as a biomarker for pathological conditions involving fibrosis and chronic inflammation. Beyond its established role in assessing liver fibrosis, HA is increasingly recognized as a potential marker for multi-organ dysfunction, particularly in cardio-hepato-renal syndromes, where the heart, liver, and kidneys are simultaneously affected [27].

HA is composed of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. It is synthesized by hyaluronan synthases (HAS1, HAS2, HAS3), and degraded by hyaluronidases. In physiological states, HA is rapidly cleared from circulation, primarily by hepatic sinusoidal endothelial cells, and to a lesser extent by the kidneys [27]. In conditions such as liver fibrosis or CKD, HA metabolism is altered. Increased production by activated fibroblasts and reduced clearance lead to elevated circulating levels, reflecting extracellular matrix deposition and tissue remodelling [28].

Role in Liver Disease

HA is widely used as a non-invasive biomarker for staging liver fibrosis and cirrhosis. The involving mechanism is activation of hepatic stellate cells in liver injury from viral

hepatitis, alcoholic liver disease, or non-alcoholic steatohepatitis. Therefore, its clinical utility is in analysis of liver fibrosis, where impaired hepatic clearance results in HA accumulation in blood, correlating with fibrosis severity [27]. Additionally, it is a part of diagnostic panels, part of the Enhanced Liver Fibrosis (ELF) test, which helps to predict progression of fibrosis to cirrhosis.

Role in Cardiovascular and Renal Diseases

In chronic heart failure, venous congestion and hypoperfusion can induce liver damage, leading to congestive hepatopathy. This condition promotes fibrotic changes and increases HA levels [27] . In advanced CKD, decreased renal clearance of HA contributes to elevated serum concentrations. High HA levels in these patients have been linked to systemic inflammation, vascular stiffness, and adverse cardiovascular outcomes [28]. Thus, HA reflects both hepatic congestion and renal dysfunction, serving as a marker of systemic congestion and multi-organ stress.

Potential Role in Cardio-Hepato-Renal Syndrome

Cardio-hepato-renal syndrome involves a dynamic interplay where dysfunction of one organ exacerbates the failure of others. Elevated HA in this context reflects increased synthesis due to fibrosis, and reduced clearance by the liver and kidneys. When combined with other biomarkers such as NT-proBNP, creatinine, and bilirubin, HA provides a more comprehensive picture of disease severity and prognosis.

Hyaluronic acid is a versatile biomolecule with diagnostic and prognostic potential across several organ systems. Its structure and metabolism allow it to serve as a sensitive indicator of fibrotic processes, particularly in liver disease, heart failure, and CKD. Although not disease-specific, its integration into multimarker panels may enhance clinical assessment of cardio-hepato-renal dysfunction and improve patient management.

Matrix Metalloproteinase-9 (MMP-9) as a Biomarker in Atrial Remodelling and Atrial Fibrillation

Matrix Metalloproteinase-9 (MMP-9), also known as gelatinase B, is a zinc-dependent endopeptidase belonging to the matrix metalloproteinase family. These enzymes play a central role in the degradation of extracellular matrix (ECM) components, thereby contributing to both physiological tissue remodelling and pathological processes such as inflammation and fibrosis [29]. MMP-9 is synthesized as an inactive proenzyme (proMMP-9) and becomes active after proteolytic cleavage. Its activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs), particularly TIMP-1. Serum levels of MMP-9 can be measured using ELISA assays, with normal values ranging between 14.3-34.6 ng/mL in women and 19.8-99.5 ng/mL in men. MMP-9 is produced by neutrophils, macrophages, fibroblasts, and monocytes, reflecting its broad role in immune and fibrotic responses [29].

Clinical significance of MMP-9 is primarily in atrial fibrillation (AF), particularly in relation to atrial remodelling and fibrosis. Studies have shown that progression from paroxysmal to persistent AF correlates with increased IL-6 levels and a higher MMP-9/TIMP-1 ratio, highlighting its role in atrial inflammation and fibrosis [30]. Increased MMP-9 expression has been observed in atrial tissue of AF patients, suggesting its involvement in atrial dilation and structural remodelling [31]. Clinical studies demonstrate significantly higher serum MMP-9 levels in AF patients compared to healthy individuals, with levels rising progressively across paroxysmal, persistent, and permanent AF stages [32] . Dysregulation of the MMP/TIMP system has also been linked to thrombogenesis in AF, suggesting a potential role in thromboembolic risk [33] . Elevated serum MMP-9 levels have been identified as an independent predictor of AF recurrence following catheter ablation, underscoring its prognostic utility [34]. Collectively, these findings position MMP-9 as a promising biomarker for atrial remodelling, AF progression, and recurrence risk.

Table 1. Comparative Overview of Emerging Biomarkers in Cardiovascular and Multiorgan Dysfunction *(Table created by the authors using AI)*

Biomarker	Biochemistry / Structure	Pathophysiology	Clinical Significance	Applications	Limitations
Ischemia-Modified Albumin (IMA)	Altered albumin with reduced cobalt-binding capacity	ROS modify albumin N-terminus during ischemia	Early marker of myocardial ischemia before necrosis	ACS triage, combined with ECG/troponins	Non-specific; rises in liver disease, renal dysfunction, infections
Soluble ST2 (sST2)	Member of IL-1 receptor family; soluble isoform	Acts as decoy receptor for IL-33, blocking cardioprotective signalling	Strong prognostic biomarker in HF and CAD	Risk stratification, therapy guidance, incorporated in HF risk scores	Not diagnostic; reflects prognosis, not etiology
Galectin-3 (Gal-3)	β-galactoside-binding lectin, chimera-type	Promotes fibroblast proliferation, collagen deposition, inflammation	FDA-approved prognostic biomarker in HF	Risk stratification, antifibrotic therapy guidance, multimarker strategies	Not disease-specific; overlaps with systemic inflammation
Thrombin–Antithrombin Complex (TAT)	Complex of thrombin bound to antithrombin	Reflects real-time thrombin generation and endothelial dysfunction	Sensitive marker of hypercoagulability	Monitoring DIC, sepsis, cancer-associated thrombosis, anticoagulant therapy	Assay variability; influenced by systemic inflammation
Neutrophil Gelatinase-Associated Lipocalin (NGAL)	25-kDa glycoprotein, lipocalin family	Released by tubular epithelial cells and neutrophils; iron-scavenging	Earliest marker of AKI (2–4h post-injury)	Cardiorenal syndrome, post-cardiac surgery, sepsis	Not specific to renal injury; rises in systemic inflammation
Hyaluronic Acid (HA)	Glycosaminoglycan, ECM component	Produced by hepatic stellate cells; impaired clearance in liver/kidney disease	Elevated in hepatic fibrosis, systemic congestion	Marker of cardio-hepato-renal dysfunction, guides decongestive therapy	Non-specific; reflects generalized ECM turnover
Matrix Metalloproteinase-9 (MMP-9)	Zinc-dependent endopeptidase (gelatinase B)	Degrades ECM (collagen IV/V, fibronectin); imbalance with TIMP-1 drives fibrosis	Implicated in atrial remodelling and AF progression	Biomarker for AF progression, recurrence after ablation, antifibrotic target	Requires standardization; influenced by inflammation and cytokines

Pathophysiologically, MMP-9 contributes to atrial remodelling by degrading key ECM components such as type IV and V collagen, fibronectin, and gelatine. This degradation facilitates structural changes in the atrial myocardium, including fibrosis, dilation, and inflammation [29]. By activating cytokines and chemokines, MMP-9 amplifies the

fibroinflammatory process within the atria, leading to both structural and electrical remodelling. Theese changes are considered central to the concept of atrial cardiomyopathy, a pathological substrate strongly associated with the onset and progression of AF. The imbalance between MMP-9 and TIMP-1 activity is particularly important, as excessive MMP-9 activation promotes fibrosis and remodelling, while reduced TIMP-1 activity fails to counteract this process [31] .

Considering clinical application, MMP-9 holds promise as a biomarker and therapeutic target in atrial fibrillation. Its biomarker role is in detecting and monitoring atrial fibrosis, inflammation, and remodelling, predicting AF progression from paroxysmal to persistent and permanent forms [34]. Its therapeutic potential lies in possibility of acting

as a monitor of antifibrotic therapies. Restoring balance in the MMP-9/TIMP-1 system could reduce atrial remodelling and thrombogenesis in AF patients. Thus, monitoring serum MMP-9 levels may guide both risk stratification and therapeutic interventions in atrial fibrillation.

Matrix metalloproteinase-9 is a key mediator of extracellular matrix remodelling and plays a pivotal role in the pathophysiology of atrial fibrillation. Elevated levels are associated with atrial fibrosis, dilation, and progression of AF, as well as increased risk of recurrence after ablation. While further validation is needed, MMP-9 represents a promising biomarker for early detection, monitoring, and therapeutic targeting in atrial fibrillation.

Conclusion

The integrated perspective underscores the future of multimarker strategies. By combining markers of ischemia, remodeling, coagulation, renal injury, and systemic fibrosis, clinicians can achieve more precise risk stratification, earlier intervention, and personalized management across cardiovascular and multi-organ disease.

The future of cardio-hepato-renal medicine lies in moving beyond fragmented diagnostics toward an integrated, biomarker-driven approach. Emerging biomarkers such as NGAL, KIM-1, Galectin-3, soluble ST2, hyaluronic acid, and MMP-9 provide mechanistic insight into inflammation, fibrosis, oxidative stress, and extracellular matrix remodelling - processes that define multiorgan dysfunction. Their use promises earlier detection of subclinical injury, sharper risk stratification, and more personalized therapeutic strategies, especially when incorporated into multimarker panels and digital health platforms.

Yet, widespread adoption requires assay standardization, validation across diverse populations, and demonstration of cost-effectiveness. Future research must emphasize longitudinal studies, biomarker-guided interventions, and composite indices that capture the dynamic interplay of the cardio-hepato-renal axis.

In conclusion, these biomarkers are more than diagnostic refinements. They represent a new lens for understanding chronic disease as a systemic process. By embracing integrative, anticipatory, and personalized care, clinicians can better protect the heart, kidneys, and liver together, advancing toward truly organ-preserving medicine.

Conflict of interest statement. None declared.

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