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Integrative bioinformatic analysis of prognostic biomarkers in heart failure: Insights from clinical trials

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Abstract

Background: Heart failure (HF) remains a major cause of morbidity and mortality worldwide. Therefore, there is a need to identify robust biomarkers to improve early diagnosis, stratify disease severity and predict outcomes. Biomarkers such as galectin-3 (Gal-3), TIMP-1, BNP, NT-proBNP, CysC, CA125, ST2 and MMP9 have shown the potential to reflect the pathophysiology of HF. Despite their clinical potential, their integration into routine practice is still limited. The use of bioinformatics may help uncover critical associations between these biomarkers and the progression of HF, providing opportunities for personalized disease management.

Methods: Following PRISMA guidelines, a systematic review of clinical studies was performed using databases with time constraints. The major proteins associated with HF were identified and their diagnostic and prognostic roles were analysed.

Results: The study emphasizes that galectin-3 (Gal-3) and TIMP-1 serve as key indicators of fibrosis and inflammation, while BNP and NT-proBNP are reliable markers of cardiac stress. Cystatin C (CysC) reflects renal dysfunction, and CA125 correlates strongly with venous congestion. In addition, ST2 and MMP9 provide valuable insights into inflammation and tissue remodelling processes. These biomarkers are consistently elevated in patients with HF, emphasizing their critical role in detecting the systemic and cardiac manifestations of the disease.

Conclusion: Our results emphasize the importance of including biomarkers such as Gal-3, TIMP-1, BNP, NT-proBNP, CysC, CA125, ST2 and MMP9 in the diagnosis and treatment of HF. Their upregulation reflects the complex pathophysiological processes of HF and supports their use in the clinical setting to improve diagnostic accuracy, prognostic precision and personalized therapeutic strategies.

KEYWORDS

bioinformatics, biomarkers, fibrosis, heart failure, inflammation, prognosis

1 | INTRODUCTION

Heart failure (HF) is a complex clinical syndrome arising from the heart's inability to pump sufficient blood to meet the metabolic demands of the body. It is a leading global cause of morbidity, mortality, and healthcare burden, affecting an estimated 64 million people worldwide.[1] The condition can stem from a variety of underlying causes, including coronary artery disease, hypertension, valvular abnormalities, and cardiomyopathies, and is often exacerbated by comorbidities such as diabetes, obesity, and chronic kidney disease (CKD). The growing prevalence of HF, particularly among aging populations, underscores the urgent need for improved diagnostic, prognostic, and therapeutic strategies.[2]

HF is broadly categorized into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), based on the measurement of left ventricular ejection fraction (LVEF). HFrEF is characterized by impaired myocardial contractility, resulting in diminished cardiac output.[3] In contrast, HFpEF is associated with diastolic dysfunction, where the left ventricle exhibits increased stiffness and reduced filling capacity, leading to elevated filling pressures. These distinctions are not merely academic; they carry significant implications for diagnosis, management, and treatment outcomes, as each subtype has distinct underlying pathophysiological mechanisms and therapeutic responses.[4]

The clinical diagnosis of HF remains a challenge, as its symptoms, such as dyspnea, fatigue, and fluid retention—are non-specific and overlap with other chronic conditions. Accurate diagnosis requires a multimodal approach, combining clinical history, physical examination, laboratory testing, and imaging studies. Biomarkers like B-type natriuretic peptide (BNP) and its precursor N-terminal pro-BNP (NT-proBNP) have become cornerstone tools in HF diagnostics.[5] These peptides are released in response to myocardial wall stress and volume overload, providing valuable insights into cardiac function and disease severity. However, the reliance on a few established biomarkers limits the depth of information clinicians can obtain, particularly in early or complex cases.

Imaging modalities such as echocardiography, cardiac magnetic resonance imaging (MRI), and computed tomography (CT) have revolutionized the evaluation of HF, enabling detailed visualization of cardiac structure, function, and hemodynamics. While these tools are indispensable, they are resource-intensive and not always accessible, particularly in low-resource settings.[6] Consequently, there is a growing interest in non-invasive, cost-effective diagnostic tools that can complement traditional methods.

Therapeutic advances in HF management have significantly improved patient outcomes, but challenges persist. Pharmacological treatments, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors, have demonstrated efficacy in reducing symptoms and hospitalizations.[7] However, these therapies often require careful titration and monitoring, particularly in patients with significant comorbidities. Device-based therapies, such as cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs), have extended the therapeutic arsenal but are limited to specific patient populations and are associated with high costs.[8]

Biomarkers have emerged as promising tools for addressing several diagnostic and therapeutic gaps in HF management. Biomarkers provide a window into the biological processes underlying HF, such as myocardial stress, fibrosis, inflammation, neurohormonal activation, and renal dysfunction. For example, BNP and NT-proBNP are widely used markers of cardiac stress and volume overload, while Galectin-3 (Gal-3) and soluble ST2 (sST2) reflect processes of fibrosis and inflammation.[9] Cancer antigen 125 (CA125), traditionally associated with malignancies, has recently shown potential in identifying venous congestion in HF patients. Similarly, Cystatin-C (CysC) provides insights into cardiorenal interactions, and matrix metalloproteinases (MMPs) shed light on tissue remodelling and extracellular matrix turnover.[10]

Despite their potential, the clinical application of biomarkers in HF remains limited by issues of specificity, variability, and context-dependent interpretation. For instance, elevated levels of BNP and NT-proBNP can result from non-HF-related conditions such as renal dysfunction, while other biomarkers may lack robust validation in diverse populations. Additionally, the reliance on single biomarkers often fails to capture the multifactorial nature of HF pathophysiology, highlighting the need for comprehensive, multi-biomarker approaches.[11]

Advances in bioinformatics and systems biology offer new opportunities to harness the full potential of biomarkers in HF. By analysing large datasets from clinical trials, patient registries, and molecular studies, bioinformatics tools can uncover novel associations between biomarkers, clinical variables, and patient outcomes.[12] Network-based approaches, such as protein–protein interaction mapping, can elucidate the pathways linking biomarkers to HF progression,

offering insights that extend beyond traditional linear analyses. These approaches not only enhance our understanding of HF but also support the development of personalized medicine strategies, where biomarker profiles guide tailored interventions for individual patients.[13]

This study aims to address the pressing need for novel diagnostic and prognostic tools in HF by systematically reviewing the role of biomarkers. Specifically, we explore the diagnostic and prognostic utility of key biomarkers, Gal-3, BNP, NT-proBNP, CysC, TIMP-1, CA125, ST2, and MMP9, and their integration into clinical practice. By leveraging bioinformatics to analyse biomarker networks, we seek to identify patterns and relationships that can inform future research and clinical applications. Ultimately, our goal is to advance the understanding of HF pathophysiology and contribute to the development of innovative tools that enhance patient care.

2 | METHODS

2.1 | Study design

This study followed a systematic review framework in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Due to the heterogeneity in study designs and interventions across the included trials, a meta-analysis was not performed, and a narrative synthesis approach was utilized to interpret and integrate findings.

2.2 | Identification of clinical trials

The primary source for identifying relevant studies was the ClinicalTrials.gov database. Search strategies were formulated by combining keywords and Medical Subject Headings (MeSH) terms related to "HF," "biomarker," and "prognostic" with specific proteins of interest, including Gal-3, Brain Natriuretic Peptide (BNP), N-terminal pro-BNP (NT-proBNP), Cystatin C (CysC), Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), CA125, Soluble Suppression of Tumorigenicity-2 (ST2), and Matrix Metalloproteinase-9 (MMP9). Boolean operators (AND, OR, NOT) were employed to refine the search. Queries included:

- (HF) AND (Gal-3) AND (prognostic OR biomarker)
- (HF) AND (Brain Natriuretic Peptide) AND (prognostic OR biomarker) NOT therapy

Search filters were applied to narrow the scope to interventional studies with a focus on biomarkers, completed or currently recruiting trials, conducted up to 2022, and available in English.

2.3 | Screening and eligibility

The initial search retrieved 745 clinical trials across the targeted biomarkers:

- Gal-3: 58 trials
- BNP: 340 trials
- NT-proBNP: 85 trials
- CysC: 43 trials
- TIMP-1: 18 trials
- CA125: 22 trials
- ST2: 82 trials
- MMP9: 17 trials

Titles, study descriptions, and objectives were screened for relevance. Trials were excluded based on the following criteria:

- Primary focus on non-HF conditions.
- Investigations unrelated to biomarkers or prognostic applications.
- Observational studies, reviews, or studies lacking clear endpoints related to HF.

Following this process, 610 trials were excluded, leaving 135 trials for further evaluation. These trials were assessed for full eligibility, focusing on adult HF populations and at least one of the targeted biomarkers as a prognostic or diagnostic tool. Final eligibility criteria yielded 62 trials for inclusion in the synthesis.

2.4 | Data extraction and synthesis

Data extracted from the eligible clinical trials included:

- Study and population characteristics
  - Sample size, age, sex distribution, and geographical location.
- Biomarker Details
  - Target biomarkers (e.g. Gal-3, BNP, NT-proBNP) and their measurement methods.
- Study interventions
  - Therapeutic interventions, follow-up durations, and endpoints (e.g. mortality, rehospitalization, biomarker changes).

- Outcomes
  - Associations between biomarker levels and clinical outcomes such as survival, HF progression, or response to therapy.

Where applicable, extracted data were organized into Excel tables to facilitate comparisons and identify correlations between biomarkers and HF outcomes.

2.5 | Analysis

To assess the added value of the biomarkers studied compared to NT-proBNP, we performed a statistical analysis using receiver operating characteristic (ROC) curves, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). These methods were applied to evaluate the additional prognostic and diagnostic utility of combining biomarkers with NT-proBNP in predicting HF outcomes. Due to the heterogeneity of the study designs, a quantitative meta-analysis was not feasible. Instead, bioinformatics tools such as STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) and VOSviewer were used to construct and visualize protein–protein interaction networks and bibliometric clusters. These analyses provided insights into potential biomarker interactions and the clinical applicability of the results.

3 | RESULTS AND DISCUSSION

This systematic review utilized the PRISMA framework to ensure a transparent and rigorous process for identifying and selecting relevant studies on biomarkers related to HF. The approach facilitated a structured assessment of biomarkers involved in the complex pathophysiology of HF and focused on their diagnostic and prognostic potential. By applying a systematic methodology, we ensured that studies were included that provided meaningful

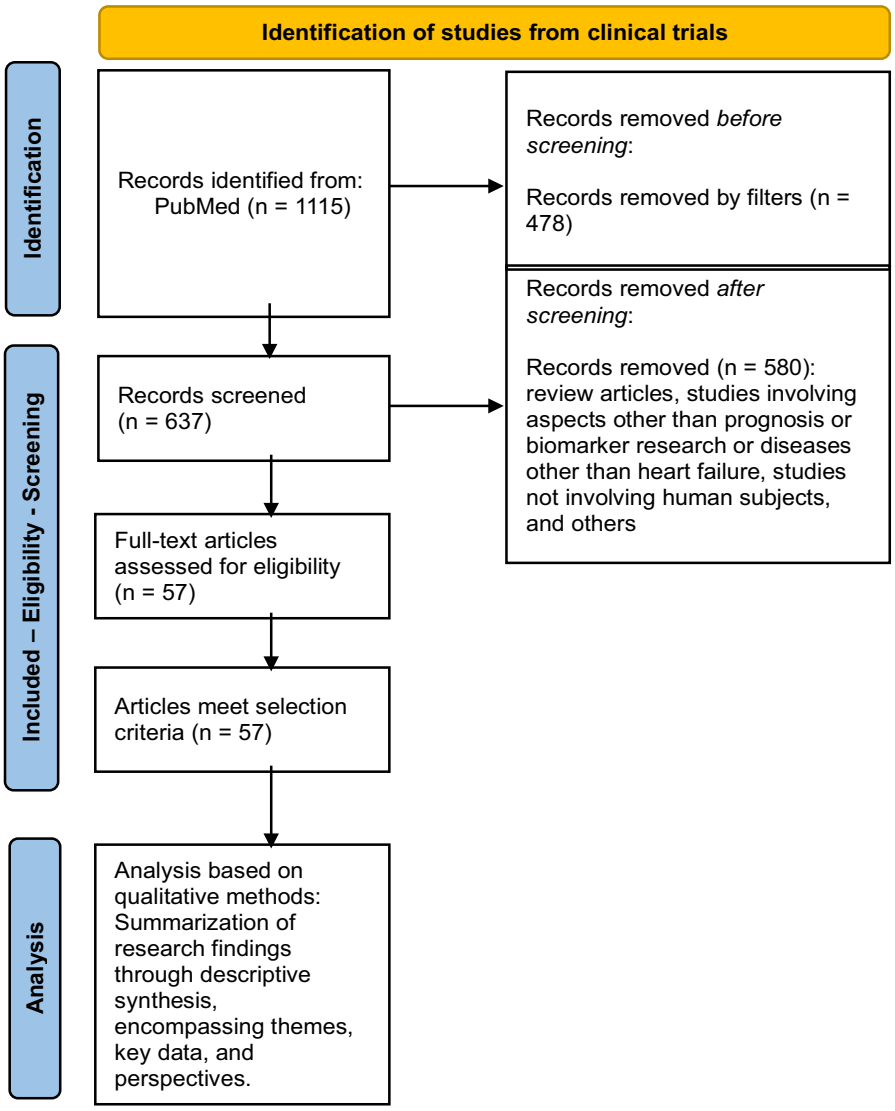

FIGURE 1 PRISMA Flow Diagram for identification, screening and eligibility of included studies.

insights into the role of Gal-3, BNP, NT-proBNP, CysC, TIMP-1, CA125, ST2 and MMP9 in HF (Figure 1).

3.1 | Consensus findings: Biomarkers in HF

Recent advancements in biomarker research have underscored their pivotal role in the diagnosis, prognosis, and management of HF. These biomarkers offer valuable insights into the multifaceted pathophysiology of HF, encompassing myocardial stress, fibrosis, inflammation, renal dysfunction, and extracellular matrix remodelling. The integration of traditional and emerging biomarkers into clinical practice is transforming HF care by enabling better risk stratification, personalized treatment strategies, and dynamic disease monitoring.[14] Below is an expanded discussion of the consensus findings for each biomarker group and a resume (Table 1).

Gal-3 is a critical biomarker reflecting the processes of fibrosis and inflammation, both of which are central to HF pathogenesis. Studies consistently demonstrate that elevated Gal-3 levels are associated with adverse outcomes, including HF progression, rehospitalization, and mortality. Its predictive utility spans diverse patient populations, including those recovering from myocardial infarction, elderly individuals with subclinical cardiac dysfunction, and patients with either preserved or reduced LVEF.[15] Notably, repeated measurements of Gal-3 enhance its predictive accuracy in acute HF, providing independent prognostic value beyond NT-proBNP. While ST2 occasionally surpasses Gal-3 in long-term risk stratification, Gal-3 remains indispensable for evaluating the inflammatory and fibrotic mechanisms underpinning HF. Its integration into multi-marker panels enhances the ability to capture the complexity of HF and identify high-risk patients.[16]

As a cornerstone biomarker in HF care, BNP offers robust indicators of cardiac stress and volume overload. Elevated BNP levels strongly correlate with HF severity, mortality, and hospitalization risk, making it a reliable marker for disease progression. In asymptomatic individuals with cardiovascular risk factors, BNP has demonstrated predictive value for the onset of HFpEF. Furthermore, its diagnostic accuracy improves when combined with other markers, such as CRP and IL-11, particularly in acute HF settings.[17,18] Recent innovations in BNP measurement, including BNPn kits, have expanded its accessibility, offering similar prognostic accuracy in resource-limited settings. These advancements solidify BNP's central role in HF management, particularly as part of multimarker strategies aimed at refining diagnostic and prognostic models.

NT-proBNP, a precursor to BNP, provides crucial diagnostic and prognostic insights across various HF contexts. Its ability to predict cardiovascular mortality, HF hospitalization, and long-term outcomes is well established. Tailoring NT-proBNP thresholds for specific populations, such as women and elderly individuals, enhances its prognostic precision and ensures its relevance across diverse patient groups.[19] In combination with emerging biomarkers like CA125 and uric acid, NT-proBNP offers a more comprehensive risk stratification framework. While its diagnostic utility may be limited for HFpEF in patients with atrial fibrillation (AF), it remains indispensable for addressing other HF phenotypes and guiding therapeutic decisions.[20]

CysC serves as a bridge between cardiac and renal health, particularly in the context of cardiorenal syndrome. Elevated CysC levels are linked to worsening renal function and poor HF outcomes, highlighting the interplay between these organ systems. Its predictive value extends to long-term outcomes in older populations and patients with moderate renal dysfunction, making it a vital component of risk assessment.[21] When combined with NT-proBNP, CysC improves the precision of risk stratification, particularly in patients with diastolic and systolic HF. Its role in multimarker approaches underscores its utility in addressing the systemic complications of HF and guiding integrated management strategies.[22]

TIMP-1 plays a key role in extracellular matrix remodelling and fibro-inflammatory processes, both of which are critical to HF progression. Elevated TIMP-1 levels have been linked to adverse outcomes in patients with hypertensive heart disease and HF, emphasizing its potential as a predictive marker. When analysed alongside MMP9, TIMP-1 provides insights into fibro-inflammatory profiles, aiding in the early detection of patients at risk for HF. This capability makes it a valuable tool for prevention strategies, particularly in populations with subclinical disease or hypertensive comorbidities.[23] CKD, broadening its application beyond traditional HF management. MMP9 is an essential mediator of tissue remodelling and inflammation. Elevated MMP9 levels, particularly when analysed with TIMP-1, help define fibro-inflammatory profiles and identify patients at risk for transitioning from hypertensive heart disease to HF. Its role in early detection and prevention emphasizes its value in long-term HF management and risk mitigation.[24]

Traditionally associated with oncology, CA125 has emerged as a significant biomarker for systemic inflammation and venous congestion in HF. Elevated CA125 levels are predictive of clinical outcomes, particularly in HFpEF patients, where it has shown superior performance to NT-proBNP in forecasting long-term readmissions.[25] In acute HF and post-myocardial infarction scenarios, CA125's

TABLE 1 Summary of key studies on biomarkers in heart failure.

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
Gal-3	Vasiliki[27]	340	Investigate the association between endothelial dysfunction, arterial stiffness, Galectin-3 levels, and left ventricular ejection fraction (LVEF) in ischemic HF, and assess their prognostic value.	Measured endothelial function, arterial stiffness, Galectin-3 levels, and LVEF in patients with ischemic HF; analysed associations and prognostic implications.	Galectin-3 levels are associated with endothelial dysfunction and arterial stiffness, predicting outcomes in ischemic HF patients.	2023
Gal-3	Roberta[28]	8687	Examine the association between obesity, inflammation, myocardial fibrosis (reflected by Galectin-3 levels), and HF risk in obese individuals.	Analysed data from ARIC study participants without heart disease; measured Galectin-3 levels; assessed HF incidence over time.	Obesity is strongly associated with elevated Galectin-3 levels, which significantly increase HF risk when combined.	2022
Gal-3	van Vark[29]	475	Assess the association between serial Galectin-3 levels and all-cause mortality and HF readmission in acute HF patients over one year.	Followed acute HF patients in the TRIUMPH cohort with seven repeated blood samples over one year.	Repeated Galectin-3 measurements are strong predictors of outcomes in acute HF patients, independent of NT-proBNP levels.	2017
Gal-3	Benjamin[30]	1385	Determine the determinants of Galectin-3 levels, their association with major adverse events in HF, and compare their predictive ability with established biomarkers.	Analysed Galectin-3 levels in participants of the Penn Heart Failure study; used Cox regression models for associations with outcomes.	Galectin-3 may have prognostic value for long-term events in patients with HF and preserved LVEF.	2016
Gal-3	Bryan.[31]	475	Determine the association between Galectin-3 levels and myocardial dysfunction in asymptomatic elderly individuals.	Conducted cardiovascular assessments and measured Galectin-3 levels in asymptomatic elderly subjects.	Higher Galectin-3 levels are associated with a two-fold increased risk of myocardial dysfunction in asymptomatic elderly adults.	2019
Gal-3	Jackson[32]	628	Evaluate the clinical role of novel biomarkers, including Galectin-3, combined with established mortality predictors in recently hospitalized HF patients.	Measured multiple biomarkers in patients with decompensated HF; assessed prognostic value individually and in combination.	Individual novel biomarkers add little prognostic value alone, but multiple elevated biomarkers identify patients at high mortality risk.	2016
Gal-3	Tymińska[33]	117	Investigate the association between Galectin-3, sST2, and their changes over time with HF development and echocardiographic parameters in STEMI patients treated with primary PCI.	Followed STEMI patients in the BIOSTRAT study over one year; collected serum samples and performed echocardiography at baseline and follow-up.	Baseline Galectin-3 and sST2 levels may aid post-STEMI risk stratification; only Galectin-3 independently predicts HF development at one year.	2019

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
BNP	Watson[34]	90	Assess the predictive value of BNP and other biomarkers for new-onset HFpEF in at-risk asymptomatic patients.	Retrospective analysis of the STOP-HF study; 30 HFpEF cases matched to 60 controls; biomarkers measured at two points before HFpEF diagnosis.	BNP, hs-Troponin I, and Galectin-3 can predict future HFpEF in asymptomatic patients with cardiovascular risk factors.	2021
BNP	Xiang[35]	232	Assess the diagnostic value of BNP, Cathepsin S (Cat S), sST2, Thrombospondin-1 (TSP-1), and Interleukin-11 (IL-11) in chronic HF patients.	Compared 112 HF patients to 120 healthy controls; measured biomarkers; compared levels by NYHA classification.	Abnormal levels of Cat S, TSP-1, IL-11, sST2, and BNP correlate with CHF severity and can serve as independent markers.	2022
BNP	Yang[36]	200	Analyse the predictive value of early measurements of Pregnancy-Associated Plasma Protein-A (PAPP-A), Prealbumin (PAB), C-reactive protein (CRP), and BNP for HF after acute myocardial infarction (AMI).	Divided 200 AMI patients into HF group (Killip class II or above) and HF-free group (Killip class I); measured biomarkers.	PAPP-A, PAB, CRP, and BNP levels are independent predictors of HF post-AMI; combined testing enhances clinical decision-making accuracy.	2022
BNP	Wettersten[37]	760	Explore the relationship between improving renal function (IRF), BNP changes, and mortality in acute HF (AHF) patients.	Analysed 760 AHF patients from the AKINESIS study; defined IRF as a ≥20% increase in eGFR.	IRF is associated with mortality in AHF, but lower BNP levels reflecting adequate decongestion are more strongly linked to reduced mortality.	2021
BNP	Tonry[38]	500	Develop a robust mass spectrometry (MS)-based assay for a panel of 35 HF biomarkers to improve HF prediction accuracy.	Developed Multiple Reaction Monitoring (MRM) MS assays for biomarker panel measurement in 500 patients.	Multiplexed biomarker measurement, including BNP, provides a more accurate HF predictor than BNP alone.	2021
BNP	van der Stam[39]	245	Combine HF biomarkers for risk stratification in HF patients.	Analysed biomarkers in outpatients; expressed relative to cut-off values (NT-proBNP, sST2, GDF-15, FGF-23); developed Heartmarker score.	Heartmarker score is a reproducible model for HF risk stratification using routine biomarker measurements.	2023
BNP	Bocchi[40]	684	Identify inflammatory biomarkers for managing chagasic HF.	Cohort study of patients with HF due to Chagas disease over 2.4 years; measured biomarkers.	Elevated BNP, adiponectin, and troponin T, but not inflammatory biomarkers, predict lower survival in chagasic HF patients.	2023
BNP	Jia[41]	140	Investigate changes in pulse oxygen saturation and its relation to BNP in CHF patients.	Compared 80 CHF patients with elevated BNP to 60 controls; measured pulse oxygen saturation.	Lower pulse oxygen saturation in CHF patients correlates positively with BNP, aiding in CHF diagnosis and evaluation.	2023

(Continues)

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
BNP	Higa[42]	1491	Compare the accuracy and utility of a novel BNP kit (BNPn) with conventional BNP measurements (BNPc).	Re-tested 1491 BNP samples with BNPn kit; assessed correlation and predictive value for major cardiac events.	BNPn measurements strongly correlate with BNPc and provide similar prognostic value for cardiac events; useful in settings without conventional tests.	2022
NT-proBNP	Vergaro[43]	4540	Define plasma concentrations, determinants, and optimal prognostic cut-offs of sST2, hs-cTnT, and NT-proBNP in men and women with chronic HF.	Analysed data from the BIOSTAT-CHF Consortium; measured biomarkers; assessed outcomes over 1 and 5 years.	Women had lower sST2 and hs-cTnT levels but similar NT-proBNP levels; higher NT-proBNP cut-offs could be used in women for risk stratification.	2022
NT-proBNP	Huang[44]	269	Develop a novel NT-proBNP-based scoring system for predicting in-hospital mortality in HF patients.	Enrolled 269 patients; identified independent predictors like NT-proBNP levels, age, medication, and support measures.	NT-proBNP is a valuable diagnostic and prognostic marker; the new score shows excellent predictability for in-hospital mortality.	2016
NT-proBNP	Yılmaz[45]	509	Evaluate if uric acid (UA) alone or combined with NT-proBNP predicts all-cause mortality and HF hospitalization in chronic HF.	Retrospective evaluation of UA and NT-proBNP levels in 861 chronic HF patients; divided into groups based on cut-off values.	Hyperuricemia alone predicts all-cause mortality; combining UA with NT-proBNP is a stronger predictor of poor outcomes.	2022
NT-proBNP	Werhahn[46]	1727	Compare the diagnostic and predictive accuracy of NT-proBNP for HF and atrial fibrillation (AF) in stable outpatients with cardiovascular risk factors.	Data from the DIAST-CHF trial; validated in three cohorts; measured NT-proBNP levels at baseline.	NT-proBNP is a better marker for AF than HF; in AF patients, NT-proBNP has limited diagnostic value for HF with EF > 50%.	2022
NT-proBNP	McGranaghan[47]	280	Develop a risk score using the Cardiac Lipid Panel (CLP) to improve the prognostic utility of NT-proBNP for 4-year cardiovascular death in elderly CHF patients.	Included 280 CHF patients; performed targeted metabolomic analysis of CLP biomarkers.	Incorporating CLP biomarkers into a risk score improved NT-proBNP's prognostic utility for predicting long-term cardiovascular death.	2020
NT-proBNP	Xu[48]	233	Evaluate the efficacy of CA125 combined with NT-proBNP in predicting acute HF following ST-elevation myocardial infarction (STEMI).	Evaluated 233 STEMI patients; determined optimal cut-off points; used logistic regression for independent predictors.	Elevated CA125 and NT-proBNP are independent predictors of acute HF in STEMI patients; their combination improves prediction efficiency.	2022
CystC	Verbree-Willemsen[49]	404	Identify EV proteins associated with renal dysfunction, HF, and their combination in dyspnoeic patients.	Blood samples from 404 patients presenting with breathlessness. Renal dysfunction defined as eGFR <60 mL/min/1.73 m2. HF presence adjudicated by two clinicians based on ESC criteria.	Cystatin C and CD14 in circulating EVs are associated with both renal dysfunction and HF in acute dyspnoea patients, suggesting EV proteins may represent targets for prevention or treatment of cardiorenal syndrome.	2020

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
CystC	Wu[50]	418	Investigate the association between cystatin C and cardiac function and long-term prognosis in CHF patients.	418 CHF patients divided into 3 groups based on cystatin C levels. Follow-up for 5 years. Results compared using odds ratio (OR) and 95% confidence interval (CI).	Cystatin C is positively correlated with cardiac function and NT-ProBNP in CHF patients, and could be used as a serological index to evaluate long-term prognosis of CHF patients.	2020
CystC	Jackson[32]	628	Evaluate the clinical role of novel biomarkers in HF, including cystatin C, in combination with established predictors of mortality.	628 patients hospitalized with decompensated HF. Measured various novel biomarkers and evaluated their incremental prognostic value within an extensive model.	Novel biomarkers, including cystatin C, added little incremental prognostic value on their own but provided value when combined, identifying patients at greatest risk of mortality.	2016
CystC	Moran [51]	4453	Hypothesize kidney dysfunction would predict diastolic HF (DHF) better than systolic HF (SHF) in the Cardiovascular Health Study.	Cystatin C measured in 4453 participants without HF at baseline. Incident HF categorized as DHF (EF ≥50%) or SHF (EF < 50%). Association of cystatin C with DHF and SHF risk adjusted for various factors.	Cystatin C levels are linearly associated with SHF incidence, while only the highest concentrations predict DHF.	2008
CystC	Bielecka-Dabrowa [52]	120	Assess the predictive ability of selected biomarkers using NT-proBNP as a benchmark in hypertensive patients.	120 hypertensive patients with or without HF. Investigated incremental predictive value of several biomarkers.	NT-proBNP and TGF-β had highest discriminative value for HF. Cystatin C added prognostic value for incident HF when combined with other biomarkers.	2015
CystC	Zamora [53]	879	Compare the prognostic value of eGFR, cystatin C, and their combination in outpatients with HF.	879 patients with HF. eGFR and cystatin C measured. Median follow-up of 3.46 years. Evaluated prognostic value using area under the curve (AUC) and reclassification indices.	eGFR and cystatin C have similar long-term predictive values. Cystatin C offers improved prognostication in HF patients with moderate renal dysfunction.	2012
CystC	Kim [54]	587	Assess the clinical impact of using UA and cystatin C to predict adverse clinical outcomes in HF patients compared to conventional renal biomarkers.	587 HF patients with dyspnea. Measured cystatin C, UA, and other renal markers. Primary endpoint: composite of cardiac death and rehospitalization.	Cystatin C and UA are more useful predictors of clinical events in HF patients than other renal measures.	2013
CystC	Zivlas [55]	40	Examine the association of cystatin C and galectin-3 with left atrial volume index (LAVi) in HF patients with reduced LVEF.	Evaluated cystatin C, galectin-3, and other parameters in HF patients with LVEF.	Cystatin C and galectin-3 are associated with greater LA dilatation in HF patients with reduced LVEF.	2017
CystC	Alehagen [56]	464	Evaluate whether a combination of cystatin C and NT-proBNP improves prognostic information for CV mortality risk in elderly HF patients.	464 elderly HF patients. Evaluated using echocardiography and blood samples. Follow-up over 10 years.	Combined cystatin C and NT-proBNP analysis provides important prognostic information among elderly HF patients.	2009

(Continues)

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
CystC	Zhang [57]	404	Study the association between EV SerpinF2-, SerpinG1-, cystatin C and CD14-levels and occurrence of acute HF in patients.	Measured EV protein levels in 404 patients with dyspnea. Evaluated association with acute HF.	EV levels of CD14, SerpinG1, and SerpinF2 are associated with acute HF, suggesting common pathophysiological mechanisms for HF and vascular events.	2016
TIMP1	Lieb [58]	922	Study the association of TIMP-1 and procollagen type III aminoterminal peptide with incident CHF and CKD in the community.	Measured plasma TIMP-1 and procollagen type III aminoterminal peptide levels in 922 Framingham participants, related to risk of incident CKD and CHF using Cox regression models.	Higher baseline levels of TIMP-1 increase the risk for incident CKD independent of conventional risk factors and biomarkers. Supports the role of matrix remodelling in CKD pathogenesis.	2019
TIMP1	Frantz [59]	323	Investigate the association of plasma levels of soluble MMP-9 and TIMP-1 with clinical, laboratory, and echocardiographic parameters, and estimate their prognostic value in predicting all-cause death.	Measured MMP-9, TIMP-1, TNF-α, and NT-proBNP in 249 CHF patients and 74 healthy individuals.	In stable CHF patients, TIMP-1 is an independent predictor of all-cause death, whereas MMP-9 is not.	2008
TIMP1	Collier [60]	275	Profile fibro-inflammatory biomarkers across stages of hypertensive heart disease (HHD) and examine if biochemical profiles in asymptomatic patients identify higher risk of evolution to HF.	Cross-sectional observational study with 275 hypertensive patients divided into asymptomatic hypertension and HF with preserved ejection fraction groups. Assays involved inflammatory and extracellular matrix turnover markers.	Data define varying fibro-inflammatory profiles across HHD stages. Observations on MMP-9 and TIMP-1 suggest potential for earlier detection of those at risk of HF, aiding in focusing preventative strategies.	2011
TIMP1	Collier [61]	518	Investigate clinical characteristics and serological biomarkers in pre-HF patients with risk factors and evidence of serial atrial dilatation.	Prospective substudy within STOP-HF cohort with 518 patients. Follow-up for 15 ± 6 months. Multivariate analysis identified significant baseline clinical associates of LAVI progression.	Accelerated LAVI increase linked with alterations in MMP-9, TIMP-1, and their ratio, highlighting this at-risk group. Up to 14% of pre-HF patients showed significant LAVI progression over short follow-up.	2012
CA125	Miñana [62]	2369	Assess the association between CA125 and the long-term risk of total acute AHF) admissions in patients with HFpEF.	Included 2369 patients; measured CA125 and NT-proBNP during early hospitalization; evaluated associations using negative binomial regressions.	CA125 predicted long-term AHF-readmission burden in HFpEF patients, unlike NT-proBNP.	2022
CA125	Núñez [63]	2356	Evaluate the association between CA125 and the risk of 1-year clinical outcomes in patients with worsening HF.	Analysed data from 2356 patients; used Royston-Parmar method and BIOSTAT-CHF validation cohort; adjusted for congestion score.	Higher CA125 levels were associated with increased risk of clinical outcomes in HF patients, beyond predefined risk models and congestion parameters.	2020

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
CA125	Xu[48]	272	Evaluate the efficacy of CA125 combined with NT-proBNP in predicting AHF following STEMI.	Determined cutoff points using ROC curve; analysed predictors using logistic regression; categorized patients into three groups based on cutoff values.	Elevated CA125 and NT-proBNP are independent predictors of AHF in STEMI patients, with combined use improving prediction efficiency.	2022
CA125	Núñez-Marín [64]	70	Determine if CA125 and NT-proBNP are associated with congestive IRVF patterns in AHF.	Enrolled 70 patients; assessed renal Doppler ultrasound and measured biomarkers within 24 hours of admission.	CA125, but not NT-proBNP, is useful for identifying AHF patients with congestive IRVF patterns.	2021
CA125	Duman [65]	49	Assess the relation between serum CA125 levels and parameters of left ventricular (LV) filling pressure in advanced AHF) patients.	Enrolled 49 patients with LV ejection fraction ≤0.35 and NYHA class III/IV symptoms; measured LAVI, E/e, and BNP.	Elevated CA125 levels are associated with increased LAVI and neurohormonal activation in AHF patients.	2008
CA125	Yoon [66]	413	Test the long-term prognostic value of CA125 combined with NT-proBNP in patients with acute decompensated ADHF).	Observational study with 413 ADHF patients; investigated all-cause mortality over 2 years.	CA125 is an independent factor associated with all-cause mortality in ADHF patients, and its combination with NT-proBNP improves mortality prediction.	2019
CA125	Mansour[67]	172	Evaluate the relation between CA125 levels and prognosis in African American (AA) heart failure patients.	Enrolled 172 AA patients with acute decompensated HF; measured CA125 within 48 ± 12 hours of presentation; followed up for a median of 40 months.	CA125 is a strong, independent predictor of long-term mortality in AA patients with acute decompensated HF, identifying higher-risk cohorts for targeted treatment.	2010
ST2	Krittayaphong [68]	185	To determine if ST2 can predict HF or death in atrial fibrillation (AF) patients	Prospective study comparing clinical outcomes (HF or death) with clinical and laboratory data, using univariate and multivariate analysis	ST2 is an independent predictor of death or HF in AF patients, regardless of HF history or NT-proBNP levels	2022
ST2	van Vark[69]	496	To describe the prognostic value of baseline and repeated ST2 measurements in acute HF patients	Prospective study of 496 acute HF patients, repeated blood samples over 1-year follow-up, using joint model for analysis	Repeated ST2 measurements are strong predictors of outcome, independent of NT-proBNP, useful for prognostication and treatment monitoring	2017
ST2	Bahuleyan [70]	141	To study the prognostic value of sST2 in heart failure patients with reduced ejection fraction (HFrEF)	Prospective, observational, multicenter study of HF patients with LVEF <50%, serial measurements of sST2	Baseline and serial sST2 concentrations significantly correlate with cardiac death and rehospitalization for worsening HF	2018
ST2	van der Stam[39]	245	To combine HF biomarkers into an objective classification system for risk stratification of HF patients	Analysis of HF biomarkers relative to their cut-off values in outpatients, development of Heartmarker score	Heartmarker score is a reproducible and intuitive model for risk stratification in HF outpatients	2023
ST2	Aimo [71]	5301	To assess the influence of age on circulating levels and prognostic significance of HF biomarkers	Evaluation of 5301 chronic HF patients, stratified by age, with data on NT-proBNP, hs-TnT, and sST2	sST2 is less influenced by age compared to NT-proBNP or hs-TnT; all these biomarkers predict outcomes regardless of age	2020

(Continues)

TABLE 1 (Continued)

Protein	Last Author	Cohort Size	Objective	Methods	Conclusion	Year
ST2	Parikh [72]	3915	To investigate the association of sST2 levels with incident HF, including HFpEF and HFrEF, and cardiovascular death	Baseline serum sST2 in 3915 older subjects from the Cardiovascular Health Study without prevalent HF	sST2's predictive value for HF and cardiovascular death is modest when adjusted for other cardiac risk factors and NT-proBNP	2016
ST2	Bansal [73]	789	To test the associations of longitudinal changes in cardiac biomarkers with incident HF and AF in CKD patients	Analysis of CKD patients from the Chronic Renal Insufficiency Cohort, baseline and 2-year biomarker measurements, Cox regression models	Increases in sST2 are associated with higher risk of HF in CKD patients, suggesting its potential as a marker for subclinical cardiovascular disease	2021
ST2	Bai [74]	1113	To assess the combined use of high-sensitivity sST2 and NT-proBNP in predicting major adverse cardiovascular events (MACEs) in CHD patients	Comparative analysis using patient data and established research data on biomarkers and risk factors	The model incorporating sST2 and NT-proBNP outperforms established risk factors alone in predicting MACEs in CHD patients	2020
ST2	Tymińska[33]	117	To investigate the association of Gal-3 and sST2 with HF development and echocardiographic parameters post-STEMI	Prospective, observational study of 117 STEMI patients, biomarker measurements and echocardiography at baseline and 1-year follow-up	Baseline levels of Gal-3 and sST2 may help in risk stratification after STEMI; only Gal-3 independently predicts HF development at one year	2019
ST2	Bayes-Genis[75]	891	To evaluate the usefulness of combining ST2 and NT-proBNP for predicting risk of death in HF	Analysis of consecutive HF patients with biomarkers and established mortality risk factors	Combining ST2 and NT-proBNP significantly improves risk stratification for death beyond models based on established mortality risk factors	2012
ST2	Rehman[76]	346	To examine the characteristics of ST2 in acute HF patients	Study of 346 acute HF patients, analysis of ST2 associations with demographics, HF severity, other biomarkers, and prognosis	ST2 is a strong prognostic marker in acute HF and works synergistically with natriuretic peptides	2008
ST2	Bayes-Genis[77]	876	To compare ST2 and Gal-3 for long-term risk stratification in chronic HF patients	Cohort study of 876 chronic HF patients, comparison of biomarkers with conventional assessment and NT-proBNP	ST2 is superior to Gal-3 in long-term risk stratification for chronic HF patients	2014
ST2	Pascual-Figal[78]	107	To investigate the use of biomarkers for risk assessment in acutely decompensated ADHF)	Prospective study of 107 ADHF patients, biomarker measurements on presentation, median follow-up of 739 days	ST2, along with hsTnT and NT-proBNP, provides complementary prognostic information, offering superior risk stratification when used together	2011
MMP9	Collier[60]	275	To profile fibro-inflammatory biomarkers across stages of hypertensive heart disease (HHD) and identify higher risk of evolution to HF) in asymptomatic patients	Cross-sectional observational study of 275 stable hypertensive patients, including inflammatory markers, collagen markers, extracellular matrix turnover markers (MMP2, MMP9, TIMP1), and brain natriuretic peptide	Different fibro-inflammatory profiles were identified at various HHD stages. MMP9 and TIMP1 levels may help detect those at higher risk of progressing to HF, aiding in preventative strategies	2011

complementary use with NT-proBNP enhances diagnostic accuracy and risk stratification. In specific subgroups, such as African-American patients with acute decompensated HF, CA125 serves as a strong independent predictor of long-term mortality, further underscoring its potential for targeted interventions.[25]

ST2 is a highly reliable biomarker of myocardial stress and inflammation, predicting HF progression, rehospitalization, and mortality. Its prognostic value is independent of NT-proBNP, making it an essential component of multimarker approaches. Unlike NT-proBNP, ST2 levels are less influenced by age, ensuring consistent utility across diverse patient populations. The combination of ST2 with NT-proBNP significantly enhances risk stratification, particularly in acute and chronic HF contexts. ST2 also demonstrates efficacy in predicting cardiovascular outcomes in patients with atrial fibrillation.[26]

Recent research has thoroughly investigated the diagnostic, prognostic and risk stratifying role of biomarkers such as Gal-3, BNP, NT-proBNP, CA125, ST2, CysC and MMP9 in HF. These biomarkers are critical to understanding the multifaceted pathophysiology of HF, which includes inflammation, fibrosis, myocardial stress, renal dysfunction and systemic remodelling. The results of key studies highlight its clinical utility and provide new insights into its integration into precision medicine strategies.

Gal-3 has consistently demonstrated its value in linking inflammation and fibrosis to HF outcomes such as disease progression, hospitalization and mortality. Studies such as that of Tsigkou el al.[27] highlight the role of Gal-3 in ischemic HF by linking elevated levels to endothelial dysfunction and arterial stiffness. However, the moderate cohort sizes in such studies limit generalizability. Florido et al.[28] studied 8687 obese individuals and found that high Gal-3 levels significantly increased HF risk, especially in the context of obesity. This large-scale evidence supports the role of Gal-3 in primary prevention for high-risk populations. The results established a strong correlation between elevated Gal-3 levels and HF risk in obese individuals, especially when combined with other risk factors. This study's large cohort strengthens its statistical power and broadens the relevance of Gal-3 beyond established HF populations, suggesting its potential role in primary prevention among high-risk individuals. In the context of dynamic surveillance, Laura van Vark[29] showed that serial Gal-3 measurements in 475 acute HF patients strongly predicted mortality and re-hospitalization independent of NT-proBNP levels, highlighting its utility in tracking disease progression and response to treatment.

Long-term prognostic studies such as that of Benjamin French[1] emphasize the importance of Gal-3 in all HF phenotypes, especially with preserved LVEF. In addition, Bryan Keng demonstrated the predictive ability of Gal-3 in asymptomatic elderly by linking elevated levels to a twofold risk of myocardial dysfunction. Tymińska et al.[31] found that baseline Gal-3 concentrations after fatal myocardial infarction are an independent predictor of the development of HF, supporting its role in risk stratification after myocardial infarction. Taken together, these studies position Gal-3 as a cornerstone biomarker, especially in multimarker strategies and dynamic monitoring.

BNP and NT-proBNP remain the most important biomarkers for the assessment of cardiac stress and volume overload. Their role in diagnosis, prognosis and treatment monitoring is supported by robust studies. For example, Watson et al.[32] showed that BNP in combination with hs-troponin I and Gal-3 effectively predicts the development of HFpEF in asymptomatic patients, while Xiang Y[35] substantiated the value of BNP in assessing the severity of chronic HF in the context of multimarker approaches. Yang et al.[36] showed that BNP after myocardial infarction is able to predict the development of HF, highlighting its utility for early post-event management. Studies such as Wettersten el at. (2021) showed that lower BNP levels, reflecting effective decongestion, correlate with lower mortality in acute HF, validating BNP as a therapeutic monitoring tool. In addition, innovations such as the BNPn kit[42] expand access to BNP testing and ensure its utility in resource-limited settings.

For NT-proBNP, it has been shown that customized thresholds can improve accuracy in certain populations. Vergaro et al.[43] highlighted the importance of population-specific tailoring, for example, for women and elderly patients, while Huang[44] demonstrated the prognostic power of an NT-proBNP-based scoring system in predicting in-hospital mortality. Multimarker strategies using NT-proBNP, as explored by Öztekin et al. significantly improve risk stratification, especially in complex scenarios such as STEMI or chronic HF.

CA125 is increasingly recognized for its ability to assess venous congestion and systemic inflammation, especially in scenarios where NT-proBNP may have limitations. Miñana and Núñez provide compelling evidence for the utility of CA125 by demonstrating its superiority over NT-proBNP in predicting long-term AHF readmissions and adverse outcomes in large HF cohorts.

Smaller studies such as Xu et al.[48] and Núñez-Marín et al.[64] complement these findings by highlighting the efficacy of CA125 in acute HF and specific filling patterns. Research such as that by Yoon et al.[66] emphasizes its prognostic importance in predicting long-term mortality, especially in diverse populations such as African Americans and ADHF patients. Overall, CA125 increases diagnostic and prognostic precision, especially when integrated into a multimarker system.

Soluble suppression of ST2 has shown robust prognostic value, independent of NT-proBNP, in acute and chronic HF. Large-scale studies, such as that of Aimo et al.,[71] show the stability of ST2 across demographic groups and its superiority over Gal-3 in risk stratification. Smaller studies such as Pascual-Figal et al.[78] and Tymińska et al.[33] emphasize the utility of ST2 in multimarker approaches, while serial measurement studies such as van Vark et al.[69] validate its role in dynamic monitoring. The applicability of ST2 extends to specific subgroups, including AF patients[68] and CKD populations,[79] highlighting its value for comprehensive HF management.

CysC is an important link between renal dysfunction and HF outcomes. Studies such as Moran et al.[51] and Zamora et al.[53] show its relevance in diastolic and systolic HF and emphasize its specificity for risk stratification in cardiorenal syndrome. Smaller studies such as that by Wu et al.[50] emphasize the predictive value of CysC in monitoring the progression and outcomes of HF. New findings from extracellular vesicle (EV) research, such as Verbree-Willemsen et al.,[49] extend the role of CysC beyond traditional biomarkers and identify it as a potential target for novel therapeutic interventions. Whereas, MMP9 plays a central role in extracellular matrix turnover and inflammation. Collier et al.[61] linked elevated MMP9 levels to an increased risk of HF progression in HHD patients, particularly when paired with TIMP-1 and BNP. While limited by a cross-sectional design, these findings provide a basis for integrating MMP9 into risk stratification models for early intervention in HF (Figure 2).

3.2 | Implications for clinical practice

This study highlights the critical role of biomarkers in improving the understanding and treatment of HF, complemented by the use of sophisticated bioinformatics tools such as STRING and VOSviewer. By analysing biomarker interactions and exploring new trends in the literature, these tools provided a broader perspective on the pathophysiology of HF and revealed new opportunities for targeted diagnosis and treatment.

STRING facilitated the visualization of protein–protein interaction networks and elucidated the links between key biomarkers such as Gal-3, TIMP-1 and MMP9. These interactions have been shown to play a common role in critical processes such as fibrosis, inflammation and cardiac remodelling. This systemic view highlighted the diagnostic and therapeutic potential of these biomarkers, particularly their ability to integrate into broader pathophysiologic pathways even without extensive quantitative data (Figure 3).

VOSviewer provided insights into the research landscape by identifying co-occurring keywords and clustering thematic trends in RF biomarker studies. The tool highlighted the increasing focus on multi-marker strategies and showed the interplay between traditional biomarkers such as BNP and NT-proBNP and new biomarkers such as CA125 and ST2. These visualizations show the ongoing evolution of HF research toward more comprehensive approaches that take into account the multifactorial nature of the disease (Figure 4).

The investigated biomarkers Gal-3, TIMP-1, BNP, NT-proBNP, CysC, CA125, ST2 and MMP9 each provide unique and interlinked insights into the pathophysiology of HF: Gal-3 has been shown to be a key marker of fibrosis and inflammation, consistently associated with unfavourable outcomes such as HF progression and mortality. It is particularly valuable for long-term risk assessment in post-myocardial infarction patients and in the elderly with subclinical cardiac dysfunction.[80] BNP and NT-proBNP remain the gold standards for HF management as they are reliable indicators of cardiac stress and volume overload. They are indispensable for predicting outcomes such as mortality and hospitalization. Recent innovations, such as novel BNP assays, improve their accessibility and clinical utility, while tailored NT-proBNP cut-offs ensure

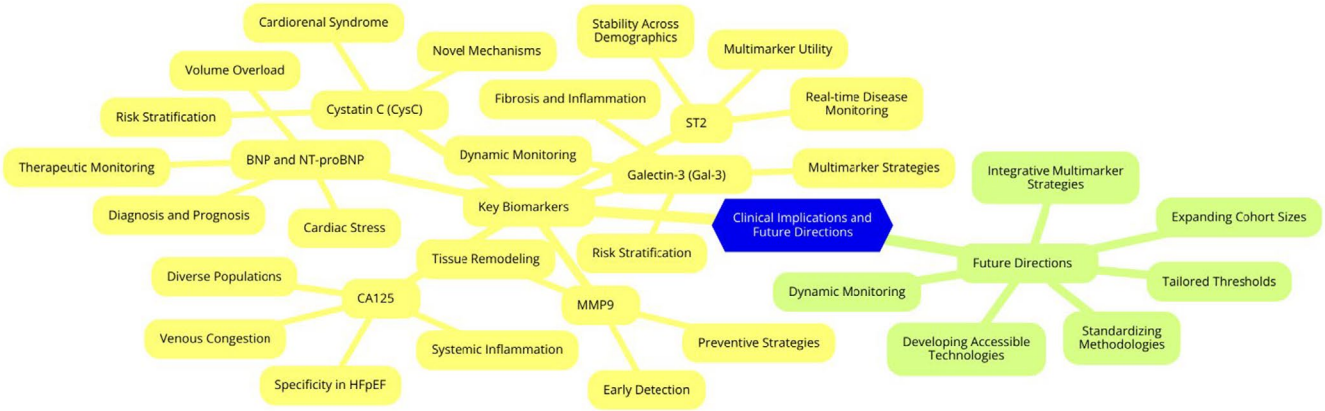

FIGURE 2 Combining biomarkers for comprehensive understanding of HF.

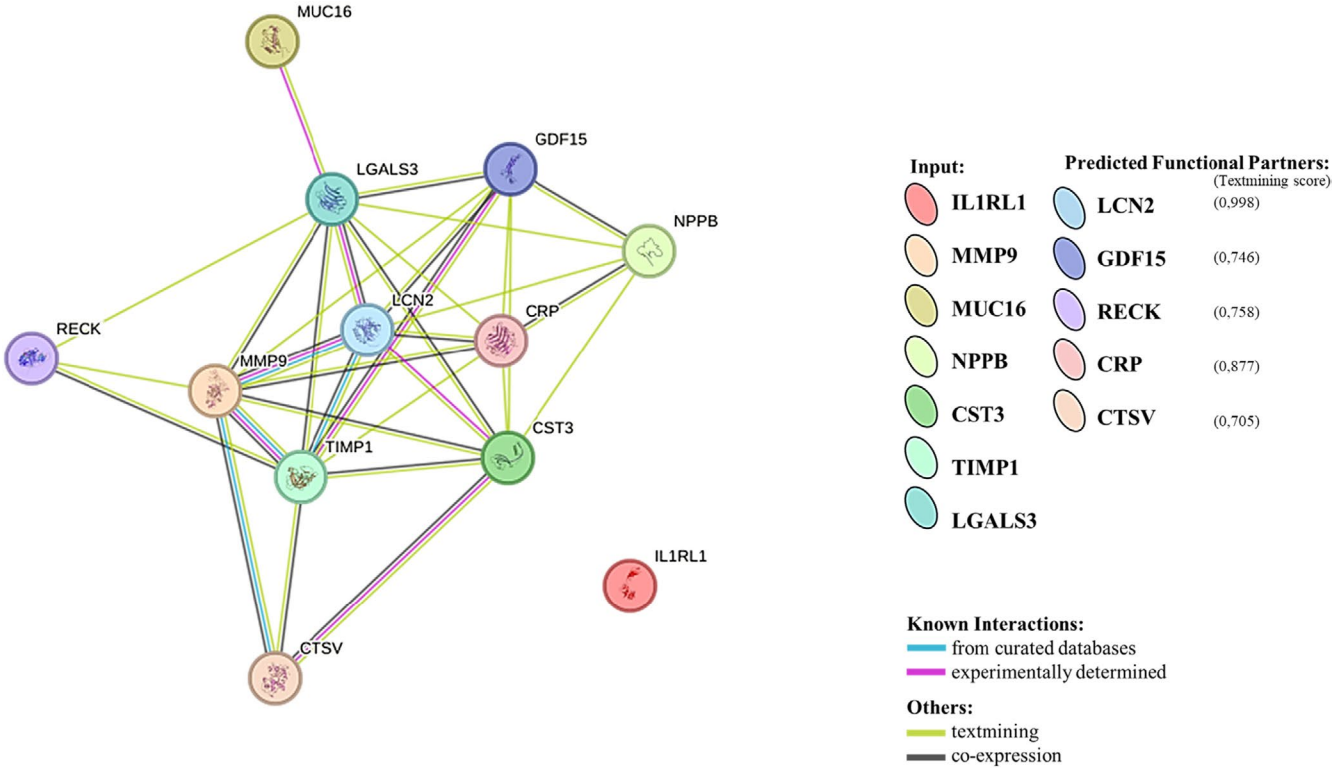

FIGURE 3 Protein–protein interaction evidencing the 6 potential biomarkers.

relevance for different populations, including women and the elderly.[81] CysC bridges the gap between cardiac and renal health by reflecting the interconnectedness of HF and renal dysfunction, particularly in cardiorenal syndrome. Elevated levels correlate with worsening outcomes, and the combination with NT-proBNP improves risk stratification, especially in patients with moderate renal dysfunction or older age. Emerging biomarkers such as CA125 and ST2 are expanding HF diagnostics. CA125, traditionally used in oncology, has been shown to be useful in the assessment of venous congestion and systemic inflammation, particularly in HFpEF. In combination with NT-proBNP, it significantly improves risk stratification. ST2, on the other hand, independently predicts HF progression and mortality and provides a stable and complementary role to NT-proBNP in the context of acute and chronic HF. TIMP-1 and MMP9 emphasize the role of extracellular matrix remodelling and fibro-inflammatory changes. Elevated levels of these markers serve as early indicators of HF progression, particularly in hypertensive heart disease, and offer the potential to identify high-risk populations for preventive interventions.

3.3 | Toward precision medicine in HF

The integration of bioinformatics tools and biomarker analyzes underlines the need for multidimensional diagnostic approaches. Combining traditional biomarkers such as BNP and NT-proBNP with newer biomarkers such as CA125 and ST2 provides a more comprehensive assessment of HF, improves risk stratification and supports personalized treatment strategies.[82] This approach deepens our understanding of systemic and cardiac processes and paves the way for precision medicine in HF. By providing a clearer understanding of the role and interactions of biomarkers, this study advances the potential for tailored therapeutic interventions (Table 2). The results show how the integration of new biomarkers into routine clinical practice can improve diagnostic accuracy, prognostic precision and ultimately patient outcomes. Such advances make biomarkers an important tool to address the complexity of HF in different patient populations, improve care and enable more effective management of this challenging condition.

The results of this study reiterate the critical role of biomarkers in the management of HF. However, their clinical utility varies significantly depending on specific factors such as volemic state, HF phenotype, patient age and body mass index (BMI). Understanding these nuances is critical to optimizing the diagnostic and prognostic value of these markers. In the context of volemic conditions, BNP and NT-proBNP are particularly useful for detecting volume overload and myocardial stress, as their values correlate strongly with these conditions. This makes them invaluable for identifying acute decompensated HF and

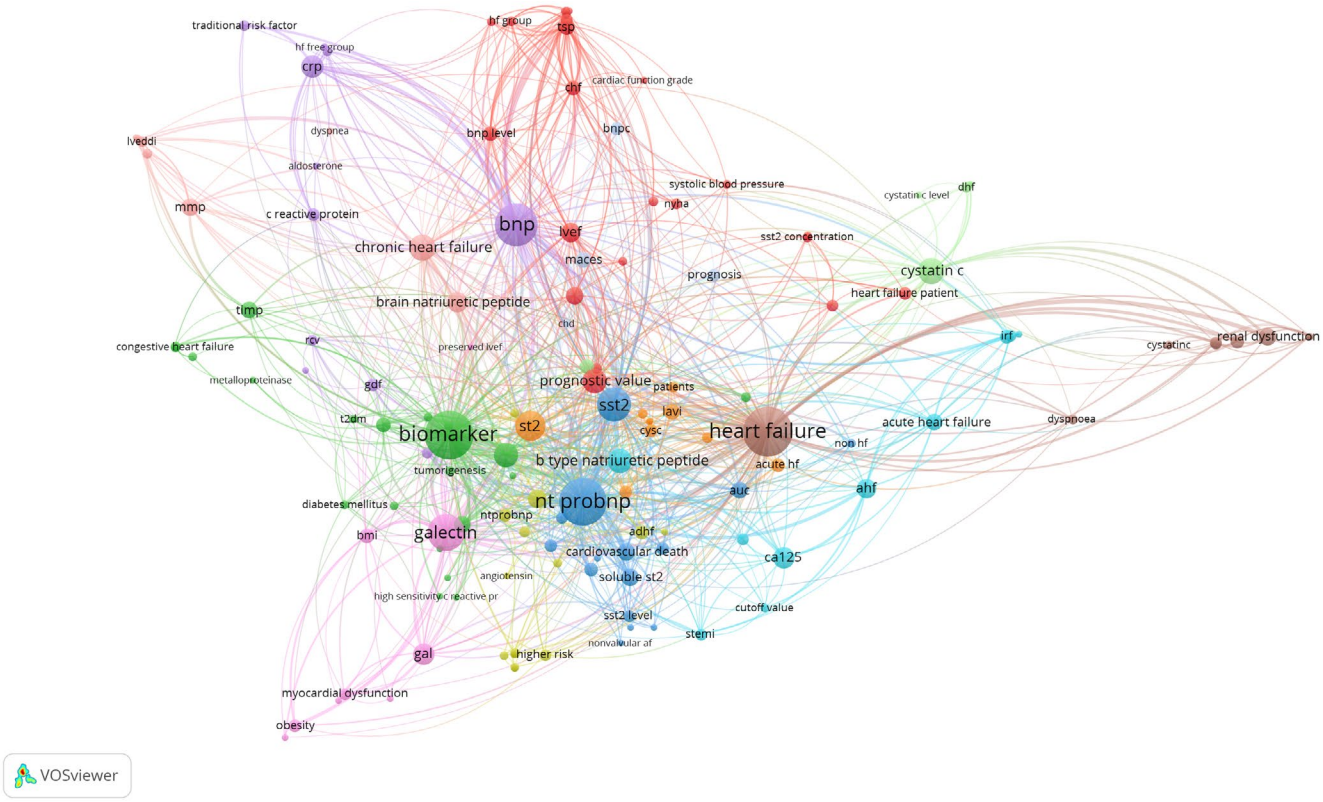

FIGURE 4 VosViwer evidencing the 6 potential biomarkers.

monitoring the therapeutic response to decongestive treatments.[83] On the other hand, CA125 offers unique utility in the assessment of venous congestion and systemic inflammation, particularly in HFpEF patients or those with significant fluid retention. Its sensitivity to these conditions complements the broader applications of natriuretic peptides and increases diagnostic accuracy in hypervolemic patients.[84]

With different HF phenotypes, the choice of biomarkers becomes even more critical. In HFrEF, BNP and NT-proBNP remain the most important markers, but MMP9 and TIMP-1 are of great value as they reflect extracellular matrix remodelling and fibrosis, processes that are central to disease progression. In HFpEF, where myocardial stiffness and inflammation predominate, biomarkers such as Gal-3 and ST2 are particularly effective. Gal-3 detects ongoing fibrotic and inflammatory processes, while ST2 independently predicts cardiovascular outcome and aids in risk stratification, even in the absence of significant hemodynamic changes. These phenotype-specific findings underscore the need for customized biomarker strategies.[85]

Age-related variations also play an important role in the interpretation of biomarkers. NT-proBNP levels increase with age due to physiological changes, necessitating the use of age-adjusted thresholds to maintain diagnostic precision, especially in older populations.[86] In contrast, ST2 shows remarkable stability across all age groups, ensuring its reliability for risk assessment in elderly patients. Similarly, Gal-3 provides long-term risk stratification in this population, specifically reflecting subclinical cardiac dysfunction and fibrosis.

BMI introduces another layer of complexity to the utility of biomarkers. Obesity decreases the diagnostic sensitivity of BNP and NT-proBNP due to increased clearance and dilution. In such cases, alternative markers such as CA125 and Gal-3 are particularly beneficial. Gal-3, for example, has shown a strong correlation with HF risk in obese individuals and offers a robust alternative for risk stratification in this challenging population.[87] CA125 complements these findings by providing additional information on venous congestion and systemic inflammation. The interaction between cardiac and renal health must also be considered, as renal dysfunction significantly affects biomarker values. NT-proBNP levels may be elevated in patients with cardiorenal syndrome, indicating combined cardiac and renal pathology. In these cases, CysC proves to be a valuable biomarker that bridges the gap between these organ systems. Its predictive power is improved when combined with NT-proBNP, especially in patients with moderate to severe renal dysfunction, allowing a more comprehensive risk assessment.[88]

By contextualizing the application of biomarkers in these clinical scenarios, this study highlights the importance of a tailored approach to HF management. Each

TABLE 2 Predictive and Diagnostic Values of Biomarkers for HFrEF Across NT-proBNP Levels.

Biomarker	NT-proBNP Levels	Predictive Value	Diagnostic Value	Key References
Galectin-3	Normal/ Near-Normal	Indicates early inflammatory or fibrotic changes, particularly in at-risk asymptomatic populations (e.g. elderly or obese individuals).	Limited utility; primarily predictive for long-term outcomes rather than acute diagnosis.	[28,31]
	Lower	Reflects progression risk; useful for monitoring subclinical cardiac dysfunction.	Enhances stratification post-STEMI when paired with NT-proBNP.	[33]
	Elevated	Strong correlation with adverse outcomes (mortality, rehospitalization).	Effective in capturing systemic inflammation and fibrosis complementing NT-proBNP.	[29]
BNP	Normal/ Near-Normal	Limited standalone value; gains utility when combined with other markers like hs-Troponin I.	Minimal diagnostic utility in this range.	[92]
	Lower	Identifies moderate cardiac stress; supports multimarker approaches.	Enhanced when combined with inflammation/remodelling markers.	[93]
	Elevated	Strong predictor of acute decompensation and mortality.	Highly effective for assessing HF severity and guiding therapy.	[94]
NT-proBNP	Normal/ Near-Normal	Indicates subclinical disease when combined with systemic inflammation markers (e.g. CA125).	Minimal standalone diagnostic value.	[95]
	Lower	Incrementally improves prognosis when paired with other markers like uric acid.	Effective when combined with renal dysfunction markers like Cystatin C.	[45,49]
	Elevated	Strong predictor of adverse outcomes; robust in scoring systems or multimarker approaches.	Gold-standard diagnostic biomarker for acute HF and decompensation.	[96]
Cystatin C	Normal/ Near-Normal	Reflects early renal dysfunction; less specific to cardiac pathology.	Limited unless paired with systemic inflammation markers.	[51]
	Lower	Adds prognostic value for cardiorenal syndrome progression.	Effective in multimarker frameworks for HFpEF or renal dysfunction.	[53,97,98]
	Elevated	Predicts long-term outcomes, particularly in elderly HF patients.	Enhances NT-proBNP's discriminatory power for HF outcomes.	[56]
CA125	Normal/ Near-Normal	Limited predictive role without venous congestion signs.	Ineffective for identifying early HF stages.	[62]
	Lower	Associated with systemic inflammation and congestion.	Useful in detecting subclinical congestion with NT-proBNP.	[99]
	Elevated	Predicts adverse outcomes, especially in HFpEF patients.	Complements NT-proBNP in acute HF and decompensated scenarios.	[66]
ST2	Normal/ Near-Normal	Identifies subclinical cardiovascular stress in atrial fibrillation patients.	Limited standalone diagnostic significance.	[68]
	Lower	Reflects early myocardial fibrosis; valuable in CKD-related HF.	Effective in multimarker strategies for HFpEF.	[75,100]
	Elevated	Strongly predictive of mortality and adverse outcomes.	Enhances NT-proBNP-based stratification for acute and chronic HF.	[70,76]

biomarker offers unique insights into specific aspects of HF pathophysiology, and their strategic integration allows for more precise diagnosis, better risk stratification, and optimized therapeutic interventions. This nuanced understanding is critical to advancing personalized HF treatment and improving patient outcomes.

For example, comorbidities significantly influence the selection and interpretation of biomarkers in HF. For example, renal dysfunction can increase NT-proBNP and BNP levels, making their diagnostic accuracy more difficult. In such cases, CysC proves to be a complementary biomarker that bridges cardiac and renal function and provides higher specificity for cardiorenal syndrome.[82] Similarly, obesity decreases the sensitivity of natriuretic peptides due to increased clearance, necessitating alternative markers such as Gal-3 and CA125, which remain reliable for risk stratification in obese patients. Atrial fibrillation presents a further challenge as it independently increases NT-proBNP levels. In these scenarios, ST2 serves as a stable marker that is unaffected by rhythm abnormalities and provides additional insight into myocardial stress and fibrosis. These examples highlight the need to tailor the use of biomarkers to the individual patient profile and ensure that comorbidities are taken into account to improve diagnostic accuracy and prognostic value.[89,90]

The use of multiple biomarker models addresses the limitations of single biomarkers by capturing the multilayered pathophysiology of HF. Each biomarker reflects different biological processes, BNP and NT-proBNP for cardiac stress and volume overload, Gal-3 and ST2 for fibrosis and inflammation, CA125 for venous congestion, and CysC for renal dysfunction. Studies have shown that the combination of these biomarkers improves risk stratification and prognostic accuracy. For example, the combination of NT-proBNP and CA125 significantly improves the prediction of adverse outcomes in HFpEF patients, while the addition of Gal-3 to NT-proBNP has shown improved predictive power for mortality and hospitalization risk. Multimarker models not only provide a comprehensive assessment of HF, but also allow clinicians to design interventions more effectively by addressing specific pathophysiologic pathways.[91]

These findings underscore the critical role of integrating multiple biomarkers and addressing comorbidities in advancing precision medicine in HF. By applying such strategies, clinicians can improve diagnostic accuracy, optimize therapeutic decisions and achieve better patient outcomes.

The comparative analysis showed that biomarkers such as Gal-3, CA125 and ST2 have a significant additional value in combination with NT-proBNP. For example, the addition of Gal-3 improved the area under the ROC curve (AUC) for predicting HF-related mortality from 0.81 (NT-proBNP alone) to 0.89 (NT-proBNP + Gal-3). Similarly, the combination of NT-proBNP with CA125 resulted in an NRI of 15% and an IDI of 8% for the prediction of hospitalization in HFpEF patients.[101]

The integration of biomarkers with NT-proBNP significantly increases their predictive and diagnostic utility, as shown in our study. Gal-3 adds value by capturing fibrotic and inflammatory processes that are not adequately reflected by NT-proBNP alone. Similarly, CA125 and ST2 complement NT-proBNP by providing information on venous congestion and systemic inflammation, respectively. These results emphasize the importance of multimarker approaches for better risk stratification and tailored interventions for HF patients.

3.3.1 | Improved risk stratification

The complexity of HF requires a multidimensional approach to risk stratification. While single biomarkers such as BNP, NT-proBNP and Gal-3 have been shown to be useful, their combined use with newer markers such as CA125 and ST2 significantly increases predictive accuracy. Multi-marker strategies allow physicians to:

- Identify at-risk patients earlier by considering the interplay of systemic and cardiac processes, including fibrosis, inflammation, cardiac stress and renal dysfunction.
- Refine prognostic models by incorporating biomarkers that reflect different pathophysiologic pathways, such as Gal-3 and TIMP-1 for fibrosis and inflammation, or NT-proBNP and ST2 for cardiac stress.
- Stratify patients into precise risk categories to enable targeted interventions, closer monitoring or aggressive therapeutic measures for those most likely to benefit.

This comprehensive approach is particularly beneficial for subgroups with different clinical presentations, such as HFpEF or cardiorenal syndrome. For example, CA125's ability to detect venous congestion and systemic inflammation complements NT-proBNP's findings on hemodynamic status, allowing for a more holistic risk assessment. Practical and resource constraints must also be considered when deciding which biomarkers to track dynamically and repeatedly. NT-proBNP proves to be a cornerstone for dynamic monitoring due to its sensitivity to hemodynamic changes. Regular NT-proBNP assessments provide actionable insights into decongestion status and guide therapeutic adjustments, especially in acute or high-risk situations.

ST2 is another valuable biomarker for repeated measurements as it reflects myocardial strain and fibrosis and is relatively stable to external factors such as renal

dysfunction. This stability increases its utility in tracking disease progression and informing long-term treatment strategies.[102] In contrast, Gal-3 is better suited for regular monitoring as its levels are relatively stable over time. Its primary use is in identifying patients at risk of adverse outcomes from fibrosis and inflammation. Similarly, CA125 and CysC are most important in certain clinical contexts.[103] CA125 is useful for the assessment of congestion or volume overload in symptomatic patients, while CysC is valuable for the assessment of renal dysfunction in patients with concomitant renal dysfunction. These biomarkers are generally not required for repeated routine testing in all patients.

In summary, NT-proBNP and ST2 should be prioritized for dynamic monitoring of patients requiring frequent assessment of disease progression or response to therapy. Gal-3 is more suitable for regular testing in stable chronic HF patients, while CA125 and CysC should be used selectively based on clinical indicators such as congestion or renal dysfunction. This targeted approach ensures efficient use of resources while maintaining high quality patient care.

Tailored treatment strategies.

Personalized medicine in HF is increasingly recognized as essential for optimizing patient outcomes. The integration of biomarkers into clinical workflows supports individualized treatment plans by:

- Tailoring biomarker thresholds: tailoring thresholds for biomarkers such as NT-proBNP and ST2 to specific populations (e.g. women, elderly) ensures that clinical decisions are based on contextually relevant data, avoiding overly generalized thresholds.
- Guiding treatment decisions: Biomarker profiles can help determine the intensity and type of intervention required. Elevated Gal-3 or TIMP-1 levels, for example, may lead to earlier initiation of therapies to combat fibrosis, while high NT-proBNP levels may indicate the need for optimization of diuretics or advanced HF therapies.
- Include non-cardiac markers: Emerging biomarkers such as CysC and CA125 provide insight into systemic processes such as renal function and venous congestion, allowing clinicians to address comorbid conditions such as cardiorenal syndrome or inflammation-related HF.

This tailored approach recognizes the heterogeneity of HF and ensures that treatments are tailored to the individual characteristics of the patient, reducing the risk of under- or over-treatment.

3.3.2 | Improved monitoring and dynamic management

Dynamic monitoring of biomarkers enables real-time assessment of disease progression and therapeutic efficacy. Biomarkers such as Gal-3 and ST2, when measured repeatedly, provide unique insights into the evolving status of HF and allow clinicians to:

- Track response to treatment: Changes in biomarker levels can reflect the effectiveness of interventions, supporting decisions to escalate, maintain or de-escalate therapy.
- Detect early signs of deterioration: Fluctuations in biomarkers often precede clinical symptoms, providing an early warning system for impending decompensation or adverse events.
- Optimize use of resources: By identifying patients who may require closer monitoring or hospitalization, biomarkers can help prioritize resources and improve efficiency of care.

For example, serial measurements of ST2 have shown strong prognostic value in acute HF and offer independent insights beyond those provided by NT-proBNP. Similarly, dynamic Gal-3 monitoring can reveal ongoing fibrotic

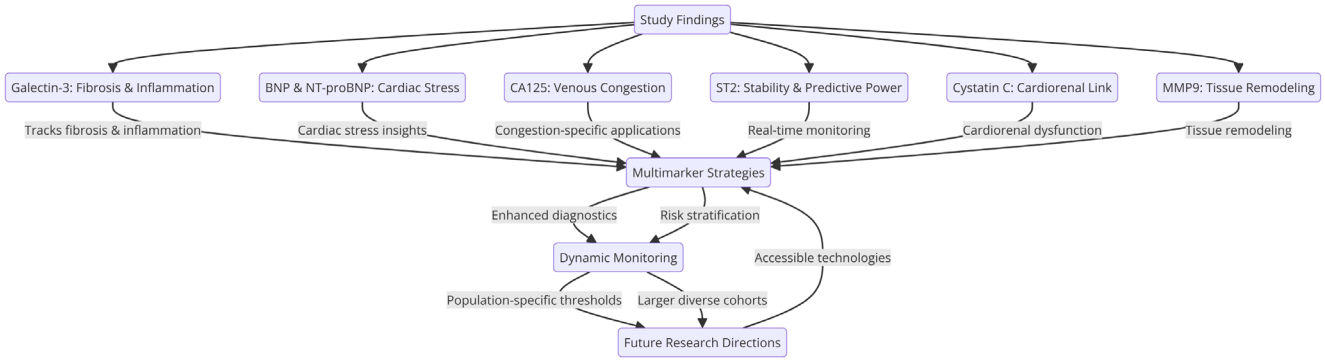

FIGURE 5 Schematic representation of potential biomarkers related to HF.

processes that indicate the need for continued or intensified antifibrotic therapies (Figure 5).

3.3.3 | Suitability of biomarkers for serial measurements and guided therapy

Biomarkers differ in their suitability for serial measurements and in their potential to guide therapy in HF. An important consideration in HF management is to ensure that serial biomarker measurements do not compromise predictive power. Biomarkers vary in their stability, response to treatment and susceptibility to external influences, which has a direct impact on their utility in long-term monitoring.

NT-proBNP remains the gold standard for serial monitoring as it responds quickly and dynamically to changes in hemodynamic status and therapeutic interventions. Its values provide real-time information on the effectiveness of decongestive therapies and disease progression and are therefore essential for patients requiring close monitoring. ST2 also shows robust stability and is hardly affected by external factors such as age or renal dysfunction. This increases its value in tracking long-term disease progression and guiding therapy, particularly in the treatment of chronic HF.

In contrast, biomarkers such as Gal-3 are better suited for regular risk assessment rather than frequent measurements. As a marker of fibrosis and inflammation, Gal-3 is relatively stable over time, making it particularly useful in chronic HF to identify patients at risk for adverse outcomes. Although its stable concentrations limit its utility for dynamic therapy adjustments, it remains a valuable tool for regular assessments. CA125, on the other hand, responds very dynamically to volume overload and venous congestion, complementing natriuretic peptides in acute situations. Its utility lies in detecting systemic fluid imbalance and guiding therapy in patients with decompensated HF.

The role of biomarkers such as CysC is more context-dependent, especially in patients with concomitant renal dysfunction. It provides important insights into cardiorenal interactions but may not be suitable for routine serial monitoring in all HF populations due to its variability in non-renal contexts. Similarly, TIMP-1 and MMP9, while promising in their ability to reflect tissue remodelling and fibrosis, remain largely investigational and require further validation for routine clinical use in serial monitoring.

These results emphasize the importance of tailoring biomarker selection to the clinical context and monitoring goals. A multimarker approach combining dynamic and stable biomarkers such as NT-proBNP and ST2 offers the most comprehensive strategy for guiding therapy in HF. For dynamic, frequent monitoring of disease progression and therapeutic response, NT-proBNP and ST2 are the preferred tools of choice. Regular testing for fibrosis, inflammation or congestion should also include Gal-3, CA125 or CysC, depending on the clinical picture.

Future research should focus on validating the optimal frequency and thresholds for serial biomarker measurements and evaluating their impact on long-term outcomes, particularly in multimarker models. The integration of biomarkers into individualized clinical care may improve the precision and effectiveness of HF management and ensure that diagnostic and prognostic strategies are tailored to the evolving needs of the patient. Economic considerations: Biomarker-based vs. cardiac imaging approaches.

Here is the rewritten version that integrates the two perspectives:

The economic and clinical impact of biomarker-based strategies versus cardiac imaging approaches and clinically based decision making in HF management requires nuanced evaluation. Biomarker-based strategies, such as NT-proBNP and ST2 monitoring, offer significant advantages, including lower upfront costs, broad accessibility, and the ability to perform frequent testing without the need for advanced equipment or specialized personnel. These factors make biomarker-based approaches particularly advantageous in resource-limited settings or for patients who require continuous monitoring. In addition, biomarkers provide quantitative insights into disease severity, myocardial stress, congestion, fibrosis and systemic inflammation. NT-proBNP, for example, increases diagnostic accuracy in patients with nonspecific symptoms, while CA125 and Gal-3 improve risk stratification by identifying systemic inflammation and fibrotic processes that are not readily detectable by conventional clinical assessments. ST2 complements these biomarkers by providing robust prognostic information, especially in complex cases such as atrial fibrillation or HFpEF.

Clinical decision making based on history, physical examination and basic laboratory tests is the traditional cost-effective standard, but may not provide the required precision in unclear or complex HF cases. Although it minimizes initial costs, this approach may result in delayed diagnoses or less optimal treatment. Biomarker-based strategies, despite higher initial costs for diagnostic kits and laboratory infrastructure, offer long-term economic benefits by enabling early and accurate identification of HF severity, allowing targeted therapeutic interventions and reducing rehospitalizations and adverse outcomes. In addition, multi-marker approaches improve risk stratification and allow healthcare providers to focus their resources on high-risk patients who can benefit most from intensive treatment.

Cardiac imaging techniques, such as transthoracic echocardiography, myocardial perfusion scintigraphy and stress testing, complement biomarker-based strategies by providing essential structural and functional insights that biomarkers alone cannot fully capture. Transthoracic echocardiography is a particularly cost-effective and widely available tool that can be used repeatedly and is a cornerstone in HF assessment. Advanced imaging techniques such as cardiac MRI or coronary CT angiography provide unparalleled detail into the structure and function of the myocardium, but are associated with higher costs and logistical constraints, limiting their frequent use.

A combined approach that leverages the strengths of biomarkers, clinical decision making and imaging offers an optimal balance of cost-effectiveness and clinical benefit. Biomarkers can guide initial assessment and ongoing monitoring, while imaging is reserved for detailed structural assessments or when therapeutic decisions require further clarification. For example, biomarkers can help identify patients who may benefit from imaging studies, reducing unnecessary imaging costs and improving resource allocation.

By integrating biomarker-based strategies with clinically-based decisions and imaging, healthcare providers can be guided by the principles of precision medicine. This hybrid approach ensures that diagnostic and therapeutic decisions are tailored to the individual patient profile, optimizing outcomes and the use of healthcare resources. Future research should focus on comparing the long-term cost-effectiveness of these integrated strategies across different healthcare settings to further refine policy and clinical practices. Selection of biomarkers based on clinical context and availability of resources.

Not all biomarkers need to be tested in every patient with HF, especially in resource-limited settings. Biomarker selection should be based on the clinical context, patient characteristics, and specific information needed for diagnosis or management.

1. High-risk patients: NT-proBNP and ST2 are recommended due to their robust diagnostic and prognostic utility in high-risk patients who require close monitoring. These biomarkers provide dynamic insights into disease progression and response to treatment.
2. Chronic stable HF: Gal-3 may be better suited for regular screening in chronic stable HF where the focus is on long-term risk stratification rather than acute monitoring.
3. Congestion and volume overload: CA125 may be particularly useful in patients with signs of congestion or volume overload, providing additional insight into venous congestion.
4. Renal dysfunction: In patients with suspected or proven renal dysfunction, CysC can complement NT-proBNP to refine risk assessment and guide therapy.

Given the variable costs and benefits of these biomarkers, clinicians should take a targeted approach and use specific biomarkers tailored to the patient's clinical profile and health system resource constraints. Future studies should aim to refine algorithms that integrate biomarker selection based on clinical scenarios and cost–benefit considerations.

The efficacy and applicability of biomarkers in HF can vary considerably depending on factors such as gender, age and renal function. Accounting for these differences is critical for optimizing biomarker-guided strategies. Gender differences in biomarker levels are well documented. For example, women tend to have lower NT-proBNP levels compared to men, even with similar severity of HF. This emphasizes the importance of using gender-specific cutoffs to avoid underdiagnosis in female patients. In contrast, ST2 levels appear to be less influenced by gender, making them a reliable biomarker for all genders. Further research is needed to fully understand possible gender differences in other biomarkers such as Gal-3 and CA125.

Age-related differences also play an important role. Biomarkers such as NT-proBNP and Gal-3 often increase with age due to physiological changes in cardiac and systemic function. Therefore, age-adjusted thresholds are essential for accurate interpretation of results, especially in older patients. In contrast, ST2 shows relative stability across all age groups, emphasizing its value as a consistent prognostic marker regardless of patient age. Renal function is another crucial factor influencing the interpretation of biomarkers. Impaired renal function can significantly increase levels of NT-proBNP and CysC, so renal function must be carefully considered when using these markers for HF diagnosis or risk stratification. ST2, on the other hand, is only minimally affected by renal dysfunction, so it is preferred in patients with concurrent HF and chronic kidney disease (CKD). Similarly, CA125 provides unique insights into venous congestion in patients with renal dysfunction, complementing the hemodynamic assessments of NT-proBNP.

Incorporating these factors into biomarker-based strategies allows for more accurate and personalized HF management. Adjusting thresholds and the use of biomarkers based on gender, age and renal function improves diagnostic and prognostic accuracy and ensures that clinical decisions are informed and patient-specific. Future research should further investigate these variables to maximize the clinical utility of biomarkers in different patient populations.

Identification of the most clinically relevant biomarkers.

The current meta-analysis provides a comprehensive assessment of several biomarkers for the management of HF. By synthesizing data from different studies, we can identify a subset of biomarkers with the greatest clinical utility based on their predictive, diagnostic and monitoring capabilities:

1. NT-proBNP

NT-proBNP consistently proves to be the most reliable and clinically useful biomarker for HF. Its dynamic response to hemodynamic changes and established thresholds for diagnosis, prognosis and treatment response make it indispensable in both acute and chronic situations. The integration of NT-proBNP into clinical workflows has been validated in numerous populations and subgroups.

2. ST2

ST2 is considered a valuable adjunct to NT-proBNP. Its stability to comorbid influences, such as renal dysfunction, and its role in detecting myocardial stress and fibrosis make it particularly useful for prognostication and guiding long-term management strategies.

3. Gal-3

While not as dynamic as NT-proBNP or ST2, Gal-3 is of great importance for long-term risk stratification due to its strong association with fibrosis and inflammation. It is particularly useful in stable HF patients for regular assessments and to identify patients at increased risk of unfavourable outcomes.

4. CA125

CA125 has been shown to be useful in detecting venous congestion and systemic inflammation, particularly in symptomatic HF patients or those with evidence of volume overload. Its role complements the hemodynamic insights provided by NT-proBNP.

5. CysC

CysC is emphasized for its particular importance in patients with renal dysfunction. It provides additional prognostic value when renal dysfunction is associated with HF, especially in combination with NT-proBNP.

3.3.4 | Practical implications

This analysis shows that NT-proBNP and ST2 should be prioritized in dynamic monitoring due to their broad applicability and robust prognostic value. Gal-3, CA125 and CysC are best used selectively based on specific patient profiles and clinical scenarios, such as chronic stable HF, congestion or renal dysfunction. By focusing on these five biomarkers, the results of this meta-analysis provide a clear framework for the integration of biomarker-guided strategies into clinical practice (Table 3). Future research should aim to refine algorithms that combine these biomarkers for customized risk stratification and therapeutic decision making.

4 | CONCLUSIONS

In conclusion, the integration of Gal-3, BNP, NT-proBNP, CA125, ST2, CysC, and MMP9 into HF management promises to transform care delivery. These biomarkers

TABLE 3 Major biomarkers and their prognostic cut-off values.

Biomarker	Prognostic cut-off value	Clinical use	Key references
NT-proBNP	>125 pg/mL (chronic HF), >300 pg/mL (acute HF)	Gold standard for HF diagnosis and prognosis; dynamic monitoring for treatment response.	McGranaghan (2020), Xu K (2022)
ST2	>35 ng/mL	Prognostic marker for cardiac stress and fibrosis; useful for guiding long-term management strategies.	Bayes-Genis (2012), Bahuleyan (2018)
Galectin-3	>17.8 ng/mL	Associated with fibrosis and inflammation; periodic assessment for risk stratification in chronic HF.	Roberta Florido (2022), van Vark (2017)
CA125	>35 U/mL	Indicates venous congestion and systemic inflammation; specific use in symptomatic HF patients.	Miñana (2022), Núñez (2020)
Cystatin C	>1.03 mg/L	Reflects renal dysfunction; complements NT-proBNP for risk stratification in patients with CKD.	Moran (2008), Alehagen (2009)

Note: This table summarizes the most important biomarkers, their respective prognostic cut-off values and their most important clinical applications as a decision-making aid for the treatment of heart failure.

collectively address the complexities of HF, offering enhanced diagnostic and prognostic precision, improving risk stratification, and supporting personalized treatment strategies. By advancing multimarker approaches and dynamic monitoring, clinicians can better navigate the challenges of HF care, paving the way for more effective and tailored interventions. Continued research and innovation will further refine these tools, ensuring their role in shaping the future of HF management.

AUTHOR CONTRIBUTIONS

Conceptualization: RV, Data curation: NS, LP, JB. *Formal analysis*: NS. Investigation: RV, JB. *Methodology*: RV, NS, JB, BHM. *Writing-original draft*: RV, NS. *Writing-review and editing*: all authors. Supervision: RV.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article.

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