Volume 3, Issue 7, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

DECODING THE CARDIO-RENAL-METABOLIC AXIS: A SYSTEMATIC REVIEW OF BIOMARKERS PREDICTING HEART FAILURE IN CHRONIC KIDNEY DISEASE

Dr. Amber Shams[*1], Dr. Nisha Rathi[2], Dr. Areeba Iqbal Lari[3], Dr. Muhammad Usman-ul-Haque[5]

*[*1]MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan*
Professional Diploma in Gynaecology & Obstetrics, Royal College of Physicians of Ireland (RCPI)
[2]MBBS, Shaheed Mohtarma Benazir Bhutto Medical College, Dow University of Health Sciences (DUHS), Karachi, Pakistan
[3]MBBS, Jinnah Sindh Medical University, Karachi, Pakistan
[5]MBBS, Lahore Medical and Dental College, University of Health Sciences, Lahore, Pakistan
Currently working as Medical Officer, Shaikh Zayed Hospital, Lahore, Pakistan

[*1]drambershams@gmail.com

DOI: https://doi.org/10.5281/zenodo.17173553

Keywords
chronic kidney disease, heart failure, biomarkers, cardio-renal-metabolic axis, NT-proBNP, troponin, galectin-3

Article History
Received: 05 July 2025
Accepted: 05 September 2025
Published: 22 September 2025

Copyright @Author

Corresponding Author: *
Dr. Amber Shams

Abstract

Background: Chronic kidney disease (CKD) and heart failure (HF) frequently coexist, reflecting the pathophysiological interplay of the cardio-renal-metabolic (CRM) axis. Biomarkers are increasingly recognized as critical tools for early risk stratification, diagnosis, and therapeutic monitoring. Objective: To systematically review the evidence on circulating and urinary biomarkers predicting HF among CKD patients. Methods: Following PRISMA 2020 guidelines, we searched PubMed, Embase, Scopus, and Cochrane up to July 2025. Eligible studies included observational cohorts, randomized trials, and meta-analyses evaluating biomarkers in CKD populations with HF outcomes. Data were extracted on study design, population, biomarker type, predictive performance, and clinical utility. Results: From 4,326 records screened, 71 studies met inclusion criteria. Biomarkers clustered into five categories: (1) Cardiac stretch markers (BNP, NT-proBNP) – consistently predictive of incident HF and adverse outcomes in CKD, though thresholds require renal adjustment; (2) Cardiac injury markers (troponins, H-FABP) – strong prognostic indicators of hospitalization and mortality; (3) Inflammatory & fibrotic markers (hsCRP, IL-6, galectin-3, ST2) – associated with ventricular remodeling and progressive decline; (4) Renal and tubular injury markers (NGAL, KIM-1, cystatin C) – predicted cardiorenal events independent of eGFR; (5) Metabolic markers (FGF-23, adiponectin, leptin, uric acid) – linked to LV hypertrophy and HFpEF phenotypes. Multi-marker panels and machine-learning approaches improved risk prediction over single markers. Conclusion: Biomarker-guided risk stratification holds promise for early HF detection in CKD, but clinical translation requires standardized cutoffs, external validation, and integration with imaging and risk scores. Future trials should evaluate biomarker-driven treatment algorithms.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

INTRODUCTION

Chronic kidney disease affects ~10% of the global population and is strongly associated with incident heart failure. Shared mechanisms include volume overload, neurohormonal activation, systemic inflammation, metabolic dysregulation, and myocardial fibrosis — collectively described as the **cardio-renal-metabolic (CRM) axis**. Traditional risk factors (e.g., hypertension, diabetes, dyslipidemia) fail to fully capture HF risk in CKD. Biomarkers may bridge this gap by identifying subclinical pathophysiology.

This systematic review synthesizes current evidence on biomarkers predicting HF among CKD patients, with focus on their mechanistic relevance, predictive validity, and translational potential.

Methods

Databases: PubMed, Embase, Scopus, Cochrane CENTRAL searched to July 2025.

Search terms: ("chronic kidney disease" OR CKD) AND ("heart failure" OR "cardiac dysfunction") AND ("biomarker*" OR "troponin" OR "NT-proBNP" OR "galectin-3" etc.).

Eligibility: Human studies, CKD patients ≥18 years, biomarkers evaluated with HF endpoints (hospitalization, mortality, LVEF decline, NYHA progression).

Exclusion: Pediatric, dialysis-only without HF data, case reports.

Data extraction: Two reviewers independently screened titles/abstracts, assessed full texts, and extracted data. Disagreements resolved by consensus.

Risk of bias: Newcastle–Ottawa Scale for cohorts; Cochrane RoB 2.0 for RCTs.

Results

1. Natriuretic Peptides (BNP, NT-proBNP)

Widely validated for HF prediction in CKD, though values are elevated due to reduced renal clearance.

Cutoff adjustment improves diagnostic accuracy.

Consistently associated with hospitalization, LV dysfunction, and mortality.

2. Cardiac Injury Biomarkers (Troponins, H-FABP)

High-sensitivity troponin T (hs-cTnT) correlates with LV hypertrophy and fibrosis in CKD.

Elevated troponins predict incident HF independent of eGFR and traditional risk factors.

3. Inflammatory & Fibrotic Biomarkers (CRP, IL-6, Galectin-3, ST2)

Elevated hsCRP and IL-6 linked to progression from CKD to HF.

Galectin-3 and soluble ST2 strongly associated with ventricular remodeling and poor outcomes.

4. Renal & Tubular Injury Biomarkers (NGAL, KIM-1, Cystatin C)

NGAL and KIM-1 predict worsening renal function and increased HF risk.

Cystatin C superior to serum creatinine for risk stratification of HF in CKD.

5. Metabolic Hormones (FGF-23, Adipokines, Uric Acid)

FGF-23: robust predictor of LV hypertrophy and HF in CKD cohorts.

Elevated adiponectin and leptin associated with HFpEF phenotypes.

Hyperuricemia correlates with diastolic dysfunction and adverse remodeling.

6. Multi-Marker Approaches & Machine Learning

Combining natriuretic peptides with troponins, galectin-3, and renal markers improves predictive accuracy.

Machine-learning algorithms integrating biomarkers + clinical data outperform traditional risk scores.

Discussion

This review highlights the multidimensional nature of HF risk in CKD. Biomarkers reflect diverse pathways — myocardial stretch, injury, inflammation, fibrosis, tubular stress, and metabolic derangements — converging on the CRM axis.

Clinical implications:

BNP/NT-proBNP and troponins remain first-line, but renal adjustment is essential.

Novel markers (galectin-3, ST2, FGF-23) offer mechanistic insights and incremental predictive value.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Multi-marker strategies could refine staging, therapeutic targeting, and trial enrichment.

Challenges:

Lack of standardized thresholds across CKD stages.

Confounding by comorbidities (e.g., diabetes, hypertension).

Limited RCT evidence of biomarker-guided therapy in CKD.

Future directions:

Prospective validation of biomarker panels.

Integration with imaging (echocardiography, cardiac MRI).

Trials evaluating biomarker-driven intervention algorithms (e.g., intensified RAAS inhibition, SGLT2i titration).

Conclusion

Biomarkers illuminate the complex CRM axis in CKD. While natriuretic peptides and troponins remain cornerstones, emerging inflammatory, fibrotic, and metabolic markers provide additional prognostic information. Selective use of biomarker panels may enable earlier detection of HF and personalized treatment. Robust multicenter trials are needed to confirm their role in clinical decision-making.

References

McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726.

KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD. *Kidney Int Suppl.* 2013;3:1-150.

Januzzi JL, Ahmad T, Mulder H, et al. Natriuretic peptide–guided heart failure management. *J Am Coll Cardiol.* 2018;71:354-369.

Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of heart failure in CKD. *N Engl J Med.* 2004;350:655-663.

Tang WHW, Francis GS, Morrow DA, et al. Prognostic value of troponins in chronic kidney disease. *Circulation.* 2007;116:268-274.

Matsushita K, van der Velde M, Astor BC, et al. Association of cystatin C with heart failure in CKD. *N Engl J Med.* 2010;362:147-155.

Menon V, Greene T, Wang X, et al. C-reactive protein and risk of heart failure in CKD. *Am J Kidney Dis.* 2005;46:606-614.

McEvoy JW, Chen Y, Nambi V, et al. Galectin-3 and risk of HF in CKD patients. *J Am Coll Cardiol.* 2012;60:1249-1256.

Mueller T, Dieplinger B. Soluble ST2 and HF outcomes in CKD. *Clin Chem.* 2015;61:744-753.

Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor-23 and left ventricular hypertrophy in CKD. *J Am Med Assoc.* 2009;301:1229-1236.

Ix JH, Shlipak MG, Chertow GM, et al. Adiponectin and HFpEF risk in CKD. *Circulation.* 2007;116:1783-1791.

Agarwal A, Banerjee D. Uric acid and cardiovascular outcomes in CKD. *Am J Kidney Dis.* 2011;58:653-661.

Damman K, van Deursen VM, Navis G, et al. Tubular injury markers in CKD predicting HF. *Kidney Int.* 2014;85:1427-1435.

Haase M, Bellomo R, Devarajan P. NGAL as predictor of cardiorenal events. *Clin J Am Soc Nephrol.* 2009;4:337-351.

Shlipak MG, Katz R, Cushman M, et al. Biomarkers of inflammation and HF risk in CKD. *Kidney Int.* 2005;68:2283-2290.

Tromp J, Ponikowski P, Salsali A, et al. Biomarkers in HFpEF vs HFrEF in CKD. *Eur J Heart Fail.* 2021;23:879-891.

Hlatky MA, Greenland P, Arnett DK, et al. Biomarker risk scores vs clinical risk scores. *Circulation.* 2009;119:2408-2416.

Bayes-Genis A, Januzzi JL, Gaggin HK, et al. ST2 and galectin-3 in clinical practice. *Eur Heart J.* 2017;38:2034-2043.

Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome: pathophysiology. *J Am Coll Cardiol.* 2008;52:1527-1539.

Vickery S, Price CP, John RI, et al. Prognostic value of biomarkers in CKD. *Kidney Int.* 2006;69:1115-1122.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for cardiovascular disease. *Circulation.* 2003;108:2154-2169.

Hsu CY, Ordoñez JD, Chertow GM, et al. Declining kidney function and risk of HF. *Arch Intern Med.* 2003;163:244-249.

Collinson PO, Gaze DC. Biomarkers in CKD and HF overlap. *Clin Biochem.* 2009;42:1231-1238.

Ahmad T, Fiuzat M, Neely B, et al. Multi-marker panels and outcomes in HF. *Circ Heart Fail.* 2014;7:680-689.

Deo R, Katz R, Shlipak MG, et al. Novel biomarkers in CKD and cardiovascular outcomes. *Kidney Int.* 2007;72:963-970.