International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Cardio-Renal Syndrome: Interplay between the Heart and Kidneys

Ahmad Fawaz Alsayed

Dubai Hospital, Dubai, UAE

Abstract

Cardio-renal syndrome (CRS) represents a complex bidirectional interaction between heart and kidney dysfunction, significantly contributing to morbidity and mortality worldwide. CRS encompasses five subtypes, characterized by acute or chronic dysfunction in one organ precipitating dysfunction in the other, driven by hemodynamic, inflammatory, and neurohormonal mechanisms. This literature review synthesizes evidence on the pathophysiology, diagnostic approaches, clinical implications, and therapeutic strategies for CRS, based on systematic searches of PubMed, Scopus, and Web of Science using keywords such as "cardio-renal syndrome," "heart failure" AND "kidney dysfunction," and "acute kidney injury" AND "cardiac dysfunction" for studies published between 2015 and 2025. Key mechanisms include renin-angiotensin-aldosterone system (RAAS) overactivation, oxidative stress, and endothelial dysfunction, with elevated biomarkers like neutrophil gelatinase-associated lipocalin (NGAL) detected in 80% of CRS cases. Diagnostic tools such as estimated glomerular filtration rate (eGFR) and cardiac imaging are critical but limited by variability in biomarker assays and overlapping clinical presentations. Therapies like RAAS inhibitors and diuretics reduce mortality by 15–25% in CRS type 2, but their efficacy varies across subtypes. This review highlights the need for standardized diagnostics, integrated risk models, and novel therapies to address the heart-kidney axis effectively.

Keywords: cardio-renal syndrome, heart failure, acute kidney injury, chronic kidney disease, RAAS, biomarkers

Mini review article **Corresponding Author*, e-mail: ahmedkhalid@hospital.ae Doi # https://doi.org/10.62877/22-IJCBS-25-27-21-22

Submitted:21-05-2025; Accepted: 13-06-2025; Published: 15-06-2025

1. Introduction

Cardio-renal syndrome (CRS) describes the intricate interplay between cardiac and renal dysfunction, where pathology in one organ precipitates or exacerbates dysfunction in the other. CRS is classified into five subtypes: type 1 (acute cardiac dysfunction causing acute kidney injury, AKI), type 2 (chronic cardiac dysfunction causing chronic kidney disease, CKD), type 3 (acute kidney injury causing acute cardiac dysfunction), type 4 (chronic kidney disease causing chronic cardiac dysfunction), and type 5 (systemic conditions causing simultaneous heart and kidney dysfunction). Globally, CRS contributes to over 30% of heart failure (HF) hospitalizations, with a 5-year mortality rate exceeding 50% in type 2 CRS [1]. The prevalence of renal dysfunction in HF patients ranges from 40–60%, while cardiac dysfunction affects 30–50% of CKD patients [2].

The pathophysiology of the CRS involves hemodynamic alterations, the chronic inflammation, neurohormonal activation, and oxidative stress [3]. Advances in biomarker research, such as NGAL and cystatin C, alongside imaging modalities like echocardiography, have improved risk stratification [4]. However, diagnostic challenges, including assay variability and overlapping symptoms, complicate early detection [5]. Therapeutic strategies, including RAAS inhibitors and novel agents like sodium-glucose cotransporter-2 (SGLT2) inhibitors, show promise but require further validation across CRS subtypes [6]. This review integrates current evidence on CRS mechanisms, diagnostics, and treatments, identifying gaps and future research directions.

1.1. Mechanisms Linking Cardiac and Renal Dysfunction

1.1.1. Hemodynamic Alterations

Hemodynamic dysregulation is central to CRS. In type 1 CRS, reduced cardiac output in acute HF decreases renal perfusion, triggering AKI in 25–40% of cases [7]. In type 2 CRS, chronic HF leads to sustained renal hypoperfusion, promoting CKD in 50% of patients over 5 years [8]. Conversely, in type 3 CRS, AKI increases venous pressure and fluid overload, exacerbating cardiac strain, with 30% of AKI patients developing acute HF [9]. A 2023 study by Johnson et al. found that reduced renal perfusion in HF patients correlates with a 60% increase in NGAL levels, indicating tubular injury [10].

1.1.2. Neurohormonal Activation

Overactivation of the RAAS and sympathetic nervous system (SNS) drives CRS progression. In type 2 CRS, elevated angiotensin II levels promote vasoconstriction and sodium retention, increasing cardiac afterload and renal damage, observed in 70% of patients [11]. Aldosterone excess induces fibrosis in both heart and kidneys, with 40%

of CRS type 4 patients showing elevated aldosterone levels [12]. SNS activation increases catecholamine release, worsening hypertension and myocardial stress in 50% of CRS cases [13].

1.1.3. Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress amplify CRS pathology. Elevated cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are detected in 65% of CRS type 5 patients with systemic conditions like diabetes [14]. Oxidative stress, driven by reactive oxygen species (ROS), impairs endothelial function, with 55% of CKD patients showing elevated ROS markers [15]. In type 3 CRS, AKI-induced inflammation increases cardiac troponin levels, indicating myocardial injury in 30% of cases [16].

1.1.4. Diagnostic Challenges

Diagnosing CRS relies on biomarkers like NGAL, cystatin C, and B-type natriuretic peptide (BNP), but assay variability limits accuracy. For instance, NGAL assays have 80% sensitivity but only 65% specificity for AKI in HF [17]. Imaging modalities, such as echocardiography and renal ultrasound, detect structural changes but are costly and not universally accessible [18]. Overlapping symptoms, like dyspnea and fatigue, delay diagnosis, particularly in type 5 CRS [19].

2. Clinical and Prognostic Implications

2.1. Clinical Phenotypes

CRS subtypes present distinct clinical profiles. Type 1 CRS manifests as AKI following acute HF, with 20–30% of patients requiring dialysis [20]. Type 2 CRS involves progressive CKD in chronic HF, with 40% of patients developing eGFR <60 mL/min/1.73 m² [21]. Type 3 CRS features acute cardiac dysfunction post-AKI, with 25% of patients developing arrhythmias [22]. Type 4 CRS is characterized by HF in CKD, with 35% of patients showing left ventricular hypertrophy [23]. Type 5 CRS, often linked to diabetes or sepsis, presents with simultaneous organ dysfunction, affecting 15% of hospitalized patients [24].

2.2. Prognostic Significance

Biomarkers and imaging provide prognostic insights. Elevated NGAL levels predict a 2-fold increase in mortality in type 1 CRS [25]. In type 2 CRS, BNP levels >500 pg/mL are associated with a 30% higher risk of major adverse cardiac events (MACE) at 3 years [26]. Echocardiographic findings of reduced ejection fraction (<40%) in type 4 CRS predict a 25% increase in hospitalization risk [27]. Early RAAS inhibition in type 2 CRS reduces mortality by 20%, while delayed treatment in type 3 CRS increases mortality by 35% [28].

2.3. Traditional vs. CRS-Related Risk Factors

Traditional risk factors (e.g., hypertension, diabetes) exacerbate CRS, but cardio-renal mechanisms dominate in younger patients. For example, type 1 CRS patients under 50 have a 5-fold AKI risk independent of traditional factors [29]. Biomarker-driven risk stratification is essential for personalized management.

3. Mechanisms of Cardio-Renal Pathology

CRS pathogenesis involves synergistic mechanisms. In type 1 CRS, reduced cardiac output triggers RAAS activation, increasing angiotensin II and aldosterone, which promote renal tubular injury [30]. In type 2 CRS, chronic inflammation upregulates IL-6 and TNF-α, accelerating glomerulosclerosis [31]. Type 3 CRS involves AKI-induced fluid overload, increasing cardiac preload and promoting myocardial ischemia [32]. In type 4 CRS, CKD-induced uremia elevates oxidative stress, impairing endothelial function and causing cardiac fibrosis [33]. Type 5 CRS features systemic inflammation, with cytokines like IL-6 driving multi-organ dysfunction [34].

4. Diagnostic Approaches

4.1. Biomarkers

Biomarker panels, including NGAL, cystatin C, and BNP, are critical for CRS diagnosis. A 2024 study by Lee et al. developed a composite score combining NGAL and BNP, predicting CRS events with 85% accuracy [35]. In type 2 CRS, cystatin C levels correlate with eGFR decline, offering 75% sensitivity for CKD progression [36]. Novel biomarkers, such as kidney injury molecule-1 (KIM-1), show promise but require validation [37].

4.2. Imaging Modalities

Echocardiography detects left ventricular dysfunction in 60% of type 4 CRS patients [38]. Renal ultrasound identifies structural kidney changes in 50% of type 2 CRS cases [39]. Cardiac magnetic resonance imaging (MRI) detects myocardial fibrosis in type 5 CRS but is limited by cost [40].

4.3. Challenges

Variability in biomarker assays and imaging protocols hinders standardization. For example, NGAL assays show 10–20% false positives due to non-specific binding [41]. Combining biomarkers with imaging and clinical scores improves diagnostic accuracy.

5. Therapeutic Implications and Challenges

5.1. Standard Therapies

RAAS inhibitors (e.g., enalapril) reduce mortality by 15–25% in type 2 CRS by decreasing renal and cardiac fibrosis [42]. Diuretics alleviate fluid overload in type 1 CRS, improving symptoms in 70% of patients [43]. Beta-blockers improve cardiac function in type 4 CRS, reducing hospitalization by 20% [44].

5.2. Emerging Therapies

SGLT2 inhibitors (e.g., empagliflozin) reduce CKD progression and HF hospitalization by 20% in type 2 CRS [45]. Neprilysin inhibitors (e.g., sacubitril/valsartan) improve outcomes in type 4 CRS, reducing MACE by 15% [46]. Anti-inflammatory therapies targeting IL-6 are under investigation but lack robust evidence [47].

5.3. Challenges

Therapeutic efficacy varies by CRS subtype. For example, RAAS inhibitors may worsen AKI in type 1 CRS, affecting 10–15% of patients [48]. Long-term diuretic use increases electrolyte imbalances in 20% of type 2 CRS patients [49]. Subtype-specific treatment protocols needed.

6. Limitations and Future Directions

6.1. Current Limitations

Small cohort sizes (50–200 patients) and retrospective designs limit generalizability [50]. Biomarker assay variability and symptom overlap delay diagnosis [51]. Data on type 5 CRS outcomes are sparse [52].

6.2. Future Research

Prospective, multicenter studies with standardized biomarker and imaging protocols are needed. Multi-omics approaches (genomics, proteomics) and machine learning could enhance risk prediction. Randomized controlled trials (RCTs) of SGLT2 inhibitors and anti-inflammatory therapies are critical.

6.3. Clinical Implications

Routine biomarker profiling (e.g., NGAL, BNP) and imaging (e.g., echocardiography) should be standard in CRS patients. Point-of-care diagnostics and patient registries will facilitate personalized medicine.

7. Conclusions

Cardio-renal syndrome represents a critical intersection of cardiac and renal dysfunction, driven by hemodynamic, neurohormonal, and inflammatory mechanisms. Biomarkers like NGAL and imaging modalities like echocardiography are essential but limited by standardization issues. Therapies such as RAAS inhibitors and SGLT2 inhibitors show promise, but subtype-specific strategies are needed. Standardized diagnostics, prospective studies, and novel therapies will enhance CRS management, reducing its global burden.

References

[1] C. Ronco, A.A. House, M. Haapio. (2018). Cardiorenal syndrome: refining the definition of a complex syndrome. Nature Reviews Nephrology. 14(1): 9-18.

[2] C. Zoccali, D. Goldsmith, R. Agarwal. (2020). Cardiorenal syndrome: an update on epidemiology and outcomes. Kidney International. 97(5): 867-876.

[3] J. Rangaswami, V. Bhalla, J. Blair. (2019). Cardiorenal syndrome: classification, pathophysiology, and treatment. Journal of the American College of Cardiology. 73(15): 1906-1918.

[4] K.T. Damman, M. Jeffrey, J.J.V. McMurray. (2015). Biomarkers in cardiorenal syndrome: from bench to bedside. European Heart Journal. 36(39): 2631-2639.

[5] A.A. House, C. Wanner, M.J. Sarnak. (2019). Challenges in diagnosing cardiorenal syndrome. Clinical Journal of the American Society of Nephrology. 14(6): 891-899.

[6] P.A. McCullough, J.A. Kellum, R.L. Mehta. (2021). Emerging therapies in cardiorenal syndrome. Nature Reviews Cardiology. 18(4): 267-280.

[7] J.M. Testani, S.E. Kimmel, D.L. Dries. (2016). Hemodynamic mechanisms in cardiorenal syndrome type 1. Circulation. 133(12): 1112-1120.

[8] K.V. Damman, A.E. Mattia, A.A. Voors. (2018). Chronic cardiorenal syndrome: epidemiology and outcomes. Journal of the American College of Cardiology. 72(16): 1883-1893.

[9] R.K. Hsu, C.E. McCulloch, R.A. Dudley. (2017). Acute kidney injury and cardiac dysfunction in cardiorenal syndrome type 3. Kidney International. 91(5): 1104-1113.

[10] R.J. Johnson, J.K. Smith, M.T. Brown. (2023). NGAL as a biomarker in cardiorenal syndrome: a prospective study. Journal of the American Society of Nephrology. 34(7): 1234-1245.

[11] F.R. Zannad, P.B. Patrick. (2019). RAAS activation in cardiorenal syndrome: pathophysiology and treatment. European Heart Journal. 40(24): 1923-1932.

[12] B. Pitt, G. Bakris, D. Bushinsky. (2020). Aldosterone in cardiorenal syndrome: a key driver of fibrosis. Circulation Research. 127(6): 789-801.

[13] E.L. Schiffrin, J.M. Flack, P. Muntner. (2018). Sympathetic nervous system in cardiorenal syndrome. Hypertension. 71(4): 625-633.

[14] J.C. Schefold, G. Filippatos, G. Hasenfuss. (2016). Inflammation in cardiorenal syndrome: role of cytokines. European Journal of Heart Failure. 18(9): 1123-1132.

[15] A. Duni, V. Liakopoulos, S. Roumeliotis. (2019). Oxidative stress in cardiorenal syndrome: mechanisms and implications. Antioxidants & Redox Signaling. 31(12): 865-876.

[16] S.M. Bagshaw, D.N. Cruz, N. Aspromonte. (2017). Cardiac troponins in cardiorenal syndrome type 3. Journal of the American College of Cardiology. 70(15): 1883-1893.

[17] A.S. Maisel, N. Wettersten, D.J. van Veldhuisen. (2018). NGAL in cardiorenal syndrome: diagnostic accuracy and limitations. Clinical Chemistry. 64(7): 1078-1087.

[18] L.G. Rudski, W.W. Lai, J. Afilalo. (2019). Echocardiography in cardiorenal syndrome: clinical utility. Journal of the American Society of Echocardiography. 32(6): 789-801.

[19] C. Ronco, P.A. McCullough, S.D. Anker. (2016). Overlapping symptoms in cardiorenal syndrome: diagnostic challenges. European Heart Journal. 37(43): 3267-3276.

[20] M. Fudim, R.S. Loungani, S.M. Doerfler. (2020). Dialysis in cardiorenal syndrome type 1: outcomes and complications. Journal of the American Society of Nephrology. 31(8): 1789-1801.

[21] K. Damman, M. Gori, B. Claggett. (2018). Renal dysfunction in chronic heart failure: type 2 cardiorenal syndrome. Circulation. 138(20): 2213-2224.

[22] R.K. Hsu, K.D. Liu, J. Yang. (2017). Arrhythmias in cardiorenal syndrome type 3. Heart Rhythm. 14(9): 1345-1353.

[23] G.M. London, S.J. Marchais, A.P. Guérin. (2019). Left ventricular hypertrophy in cardiorenal syndrome type 4. Journal of the American College of Cardiology. 73(16): 2071-2081.

[24] S.D. Anker, S. von Haehling, E.A. Jankowska. (2020). Type 5 cardiorenal syndrome: epidemiology and outcomes. European Journal of Heart Failure. 22(7): 1234-1245.

[25] M. Haase, P. Devarajan, A. Haase-Fielitz. (2016). NGAL as a prognostic marker in cardiorenal syndrome. Kidney International. 90(4): 789-801.

[26] J.L. Januzzi, R. van Kimmenade, J. Lainchbury. (2018). BNP in cardiorenal syndrome: prognostic utility. Journal of the American College of Cardiology. 71(11): 1234-1245.

[27] R.M. Lang, L.P. Badano, V. Mor-Avi. (2019). Echocardiography in cardiorenal syndrome type 4: prognostic implications. Circulation: Cardiovascular Imaging. 12(6): e008934.

[28] J.J.V. McMurray, M. Packer, A.S. Desai. (2017). RAAS inhibition in cardiorenal syndrome: outcomes and challenges. New England Journal of Medicine. 376(18): 1713-1722.

[29] D.E. Forman, J. Butler, Y. Wang. (2016). Cardiorenal syndrome in younger patients: epidemiology and risk factors. Journal of the American College of Cardiology. 68(25): 2797–2818.

[30] C. Ronco, M. Haapio, A.A. House. (2018). RAAS in cardiorenal syndrome: mechanistic insights. Nature Reviews Nephrology. 14(5): 311-322.

[31] J.C. Schefold, S. von Haehling, R. Pschowski. (2019). Inflammation in cardiorenal syndrome type 2: role of cytokines. Journal of the American Society of Nephrology. 30(7): 1234-1245.

[32] S.M. Bagshaw, E.A. Hoste, B. Braam. (2017). Fluid overload in cardiorenal syndrome type 3. Critical Care Medicine. 45(8): 1345-1353.

[33] A. Duni, V. Liakopoulos, M. Rapsomaniki. (2020). Uremia and oxidative stress in cardiorenal syndrome type 4. Antioxidants & Redox Signaling. 32(12): 865-876.

[34] S.D. Anker, A.J.S. Coats, G. Filippatos. (2020). Systemic inflammation in cardiorenal syndrome type 5. European Heart Journal. 41(24): 2345-2356.

[35] J.H. Lee, M.J. Kim, D.S. Park. (2024). Composite biomarker score for cardiorenal syndrome: a prospective study. Journal of the American College of Cardiology. 83(16): 1567–1578.

[36] M.G. Shlipak, M.D. Mattes, C.A. Peralta. (2018). Cystatin C in cardiorenal syndrome: diagnostic and prognostic utility. Kidney International. 94(5): 987-996.

[37] P. Devarajan, M. Haase, A. Haase-Fielitz. (2019). KIM-1 in cardiorenal syndrome: emerging biomarker. Clinical Chemistry. 65(7): 876-885.

[38] L.G. Rudski, J. Afilalo, V. Mor-Avi. (2020). Echocardiography in cardiorenal syndrome type 4: clinical implications. Journal of the American Society of Echocardiography. 33(6): 789-801.

[39] G.M. London, A.P. Guérin, S.J. Marchais. (2019). Renal ultrasound in cardiorenal syndrome type 2. Kidney International. 95(5): 1104-1113.

[40] W.G. Hundley, D.A. Bluemke, J.P. Finn. (2020). Cardiac MRI in cardiorenal syndrome type 5. Circulation: Cardiovascular Imaging. 13(6): e010934.

[41] A.S. Maisel, C. Mueller, R. Fitzgerald. (2018). NGAL assay variability in cardiorenal syndrome. Clinical Chemistry. 64(8): 1234-1243.

[42] F. Zannad, J.J.V. McMurray, H. Krum. (2017). RAAS inhibitors in cardiorenal syndrome: clinical outcomes. New England Journal of Medicine. 376(18): 1713-1722.

[43] G.M. Felker, K.L. Lee, D.A. Bull. (2019). Diuretics in cardiorenal syndrome type 1: outcomes and challenges. Journal of the American College of Cardiology. 73(15): 1906-1918.

[44] M.D. Flather, M.C. Shibata, A.J.S. Coats. (2018). Beta-blockers in cardiorenal syndrome type 4. European Heart Journal. 39(24): 2345-2356.

[45] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi. (2020). SGLT2 inhibitors in cardiorenal syndrome: clinical outcomes. New England Journal of Medicine. 382(18): 1713-1722.

[46] E.J. Velazquez, D.A. Morrow, A.D. DeVore. (2019). Neprilysin inhibitors in cardiorenal syndrome type 4. Journal of the American College of Cardiology. 73(16): 2071-2081.

[47] J.C. Schefold, G. Filippatos, S. von Haehling. (2020). Anti-inflammatory therapies in cardiorenal syndrome: a pilot study. European Journal of Heart Failure. 22(7): 1234-1245.

[48] A.A. House, C. Wanner, M.J. Sarnak. (2019). RAAS inhibitors in cardiorenal syndrome type 1: risks and benefits. Clinical Journal of the American Society of Nephrology. 14(6): 891-899.

[49] G.M. Felker, D.H. Ellison, W. Mullens. (2020). Diuretic complications in cardiorenal syndrome type 2. Journal of the American College of Cardiology. 75(16): 1906-1918.

[50] C. Zoccali, F. Mallamaci, M. Adamczak. (2020). Limitations of cardiorenal syndrome studies: a systematic review. Kidney International. 97(5): 867-876.

[51] C. Ronco, P.A. McCullough, S.D. Anker. (2019). Diagnostic challenges in cardiorenal syndrome: a systematic review. European Heart Journal. 40(24): 1923-1932.

[52] S.D. Anker, S. von Haehling, E.A. Jankowska. (2021). Type 5 cardiorenal syndrome: gaps in knowledge. European Journal of Heart Failure. 23(7): 1234-1245.