World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Cardiorenal syndrome: A systematic review of pathophysiology, classification, biomarkers, echocardiographic strain, therapeutic strategies and prognostic implications

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World Journal of Advanced Research and Reviews, 2026, 30(01), 1206-1215

Publication history: Received on 24 February 2026; revised on 06 April 2026; accepted on 08 April 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.30.1.0843

Abstract

Background: Cardiorenal Syndrome (CRS) represents a complex bidirectional interaction between cardiac and renal dysfunction and is associated with substantial morbidity and mortality. Conventional parameters, including left ventricular ejection fraction (LVEF) and serum creatinine, are limited in detecting early subclinical dysfunction. Emerging evidence highlights the role of echocardiographic strain imaging, particularly global longitudinal strain (GLS), in identifying early myocardial impairment and improving risk stratification in CRS.

Objectives: To systematically evaluate the pathophysiology, classification, biomarkers, echocardiographic strain, therapeutic strategies, and prognostic implications of CRS across its subtypes.

Methods: A systematic search of PubMed, Embase, Scopus, and the Cochrane Library was conducted for studies published between 2005 and 2025. Randomized controlled trials, cohort studies, and observational studies involving adult patients with CRS (Types 1–5) were included. Data extraction and quality assessment were performed independently by two reviewers in accordance with PRISMA guidelines. Outcomes of interest included all-cause mortality, renal function decline, heart failure hospitalization, and the diagnostic and prognostic performance of biomarkers and strain parameters.

Results: A total of 72 studies encompassing 131,845 patients were included. CRS Type 1 and Type 2 accounted for the majority of cases (>70%) and were associated with the highest adverse event rates. The prevalence of CRS in acute heart failure ranged from 25% to 40%, with 1-year mortality exceeding 30%. Pathophysiological mechanisms extended beyond reduced cardiac output and included venous congestion, neurohormonal activation, systemic inflammation, and endothelial dysfunction.

Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C demonstrated superior early detection of renal injury compared with conventional measures, while natriuretic peptides retained strong prognostic utility.

Importantly, echocardiographic strain imaging emerged as a sensitive marker of subclinical myocardial dysfunction. GLS impairment was consistently observed even in patients with preserved LVEF and was independently associated with worsening renal function and adverse outcomes. Across studies, reduced GLS (less negative values) was associated with increased mortality and hospitalization risk (hazard ratios 1.4–2.2).

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Therapeutically, renin–angiotensin–aldosterone system inhibitors and sodium–glucose cotransporter-2 inhibitors (SGLT2 inhibitors) reduced composite cardiorenal endpoints by approximately 20–30%, while device-based therapies such as ultrafiltration were beneficial in selected refractory cases.

Conclusions: CRS is a multifaceted syndrome driven by complex hemodynamic and non-hemodynamic mechanisms and is associated with consistently poor outcomes. Integration of echocardiographic strain imaging with biomarker-based approaches enhances early detection and prognostic stratification beyond conventional measures. Emerging therapies, particularly SGLT2 inhibitors, provide significant cardiorenal protection. Future research should focus on standardized diagnostic frameworks and personalized, imaging-guided management strategies.

Keywords: Cardiorenal Syndrome; Global Longitudinal Strain; Echocardiographic Strain; Biomarkers; Heart Failure; Chronic Kidney Disease; SGLT2 Inhibitors

1. Introduction

Cardiorenal Syndrome (CRS) represents a complex clinical entity characterized by bidirectional interactions between the heart and kidneys, wherein acute or chronic dysfunction in one organ precipitates dysfunction in the other (1,2). This intricate interplay reflects shared hemodynamic, neurohormonal, and inflammatory pathways and is increasingly recognized as a major determinant of adverse clinical outcomes in patients with cardiovascular and renal disease.

CRS encompasses a heterogeneous spectrum of disorders classified into five subtypes according to the widely accepted Ronco classification, incorporating acute and chronic forms of cardiac and renal dysfunction, as well as systemic conditions affecting both organs (1). Among these, CRS Type 1 (acute heart failure leading to acute kidney injury) and Type 2 (chronic heart failure leading to chronic kidney disease) are the most prevalent and are associated with substantial morbidity, recurrent hospitalizations, and increased mortality. Epidemiological data indicate that CRS occurs in approximately 25%–40% of patients hospitalized with acute heart failure, significantly influencing both short-term and long-term outcomes (2).

The pathophysiology of CRS extends beyond traditional paradigms of reduced cardiac output and renal hypoperfusion (3,4). Emerging evidence underscores the central role of venous congestion, alongside increased intra-abdominal pressure, endothelial dysfunction, oxidative stress, and activation of neurohormonal pathways, including the renin–angiotensin–aldosterone system and sympathetic nervous system. These interrelated mechanisms contribute to a self-perpetuating cycle of cardiac and renal dysfunction, highlighting the need for early detection and targeted therapeutic strategies.

Despite advances in understanding CRS, conventional diagnostic parameters such as serum creatinine and left ventricular ejection fraction (LVEF) remain limited in their ability to detect early subclinical dysfunction (5,6). Serum creatinine is influenced by multiple non-renal factors and often rises late in the course of renal injury, whereas LVEF may remain preserved despite significant myocardial impairment, particularly in heart failure with preserved ejection fraction. Consequently, increasing attention has been directed toward novel biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and natriuretic peptides, which provide enhanced sensitivity for early detection and improved risk stratification.

In parallel, advancements in cardiac imaging have led to the emergence of echocardiographic strain analysis, particularly global longitudinal strain (GLS), as a sensitive marker of myocardial function (7-9). GLS reflects subendocardial fiber deformation and enables detection of subtle myocardial dysfunction before overt changes in LVEF become apparent. In the context of CRS, strain imaging offers a unique opportunity to identify early cardiac involvement, quantify the severity of cardiorenal interaction, and refine prognostic assessment. Accumulating evidence suggests that impaired GLS is independently associated with worsening renal function, increased hospitalization rates, and higher mortality, even among patients with preserved LVEF.

Therapeutically, the management of CRS remains challenging due to its multifactorial and heterogeneous nature. Traditional approaches have focused on diuretics and neurohormonal blockade, particularly renin–angiotensin–aldosterone system inhibitors. More recently, sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated substantial cardiorenal benefits across a broad spectrum of patients with heart failure and chronic kidney disease, representing a paradigm shift in CRS management (10-12). However, variability in therapeutic response and the lack of standardized, integrated care pathways underscore persistent gaps in clinical practice.

Given these complexities, a comprehensive synthesis of current evidence encompassing pathophysiology, classification, biomarkers, echocardiographic strain, therapeutic strategies, and prognostic implications is warranted. Therefore, the present systematic review aims to provide an updated and integrative evaluation of CRS, with particular emphasis on the emerging role of strain imaging in enhancing early diagnosis and guiding clinical management.

2. Methods

2.1. Study Design and Reporting Standards

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was predefined to ensure transparency, reproducibility, and minimization of bias.

2.2. Eligibility Criteria

Studies were selected based on the PICOS framework:

- Population: Adult patients (≥18 years) diagnosed with Cardiorenal Syndrome (Types 1–5), heart failure with renal dysfunction, or chronic kidney disease with cardiac involvement.
- Intervention/Exposure: Evaluation of pathophysiological mechanisms, biomarkers (e.g., neutrophil gelatinase-associated lipocalin [NGAL], cystatin C, natriuretic peptides), echocardiographic strain parameters (including global longitudinal strain [GLS]), and therapeutic interventions (pharmacological or device-based).
- Comparator: Standard care, absence of CRS, or comparisons between CRS subtypes or diagnostic modalities.
- Outcomes: All-cause mortality, cardiovascular mortality, heart failure hospitalization, renal function decline (e.g., change in estimated glomerular filtration rate [eGFR]), and diagnostic and prognostic performance of biomarkers and strain imaging.
- Study Design: Randomized controlled trials, prospective and retrospective cohort studies, and observational studies.

2.3. Exclusion Criteria

Pediatric populations

- Case reports and small case series (<10 patients)
- Review articles, editorials, and conference abstracts without full data
- Non-English language publications

Information Sources and Search Strategy

- A comprehensive literature search was conducted in the following electronic databases:
- PubMed/MEDLINE
- Embase
- Scopus
- Cochrane Library

The search included studies published between January 2005 and December 2025, corresponding to the modern classification era of CRS.

A combination of Medical Subject Headings (MeSH) and free-text terms was used, including: “cardiorenal syndrome,” “heart kidney interaction,” “acute kidney injury AND heart failure,” “chronic kidney disease AND cardiac dysfunction,” “biomarkers,” “NGAL,” “cystatin C,” “echocardiographic strain,” “global longitudinal strain,” and “SGLT2 inhibitors.” Boolean operators (AND/OR) were applied appropriately, and the search strategy was adapted for each database. The full electronic search strategy is provided in the Supplementary Appendix.

2.4. Study Selection

All retrieved records were imported into reference management software, and duplicate entries were removed. Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were subsequently assessed against

predefined inclusion and exclusion criteria. Discrepancies were resolved through consensus or consultation with a third reviewer.

The study selection process was documented using a PRISMA flow diagram (Figure 1).

2.5. Data Extraction

Data were independently extracted by two reviewers using a standardized data collection form. The following variables were recorded:

- Study characteristics: author, year, country, and study design
- Population characteristics: sample size, age, and comorbidities
- CRS classification (Types 1–5)
- Biomarkers assessed (e.g., NGAL, cystatin C, BNP/NT-proBNP)
- Echocardiographic parameters: LVEF and global longitudinal strain (GLS)
- Therapeutic interventions (pharmacological and device-based)
- Outcomes: mortality, hospitalization, and renal function decline
- Effect measures: hazard ratios (HR), odds ratios (OR), and corresponding confidence intervals (CI)

2.6. Quality Assessment and Risk of Bias

The methodological quality of included studies was assessed using:

- The Cochrane Risk of Bias Tool for randomized controlled trials
- The Newcastle–Ottawa Scale (NOS) for observational studies
- Studies were categorized as having low, moderate, or high risk of bias. Any disagreements were resolved by consensus.

2.7. Data Synthesis and Statistical Analysis

A qualitative (narrative) synthesis of findings was performed across included studies. Where appropriate, quantitative pooling was considered.

- Statistical heterogeneity was assessed using the I^2 statistic
- A random-effects model was planned for meta-analysis in the presence of significant heterogeneity
- Subgroup analyses were conducted based on CRS subtype and study population
- Particular emphasis was placed on:
- Diagnostic and prognostic performance of biomarkers
- Incremental value of echocardiographic strain (GLS) over conventional parameters
- Impact of therapeutic interventions on cardiorenal outcomes
- Publication bias was evaluated using funnel plots where sufficient studies were available.

2.8. Ethical Considerations

As this study is a systematic review of previously published data, ethical approval and informed consent were not required.

3. Results

3.1. Study Selection

The systematic search identified 2,558 records, of which 2,041 remained after removal of duplicates. Following title and abstract screening, 229 full-text articles were assessed for eligibility. A total of 157 studies were excluded due to lack of CRS-specific data, absence of relevant outcomes, review design, insufficient data, pediatric populations, or duplicate datasets. Ultimately, 72 studies comprising 131,845 patients were included in the qualitative synthesis, with 28 studies eligible for quantitative analysis (Figure 1, PRISMA flow diagram).

3.2. Study Characteristics

The included studies encompassed a heterogeneous population of patients with Cardiorenal Syndrome across its five subtypes. The majority were observational cohort studies, with a smaller proportion of randomized controlled trials evaluating therapeutic interventions.

CRS Type 1 and Type 2 accounted for over 70% of included populations, whereas Type 3–5 CRS were less frequently represented. Sample sizes ranged from small mechanistic cohorts to large multicenter trials exceeding 4,000 participants, with follow-up durations extending from in-hospital outcomes to long-term follow-up beyond 5 years.

3.3. Pathophysiological Insights

Across studies, CRS was consistently characterized by a complex interplay of hemodynamic and non-hemodynamic mechanisms. While reduced cardiac output and renal hypoperfusion contributed to disease progression, venous congestion emerged as a dominant driver of renal dysfunction.

Additional mechanisms included:

- Activation of the renin–angiotensin–aldosterone system (RAAS)
- Sympathetic nervous system overactivity
- Systemic inflammation and oxidative stress
- Endothelial dysfunction and microvascular impairment

These findings support a shift toward a multifactorial cardiorenal interaction model, rather than a purely forward failure paradigm.

3.4. Biomarkers in Cardiorenal Syndrome

A wide range of biomarkers were evaluated for early diagnosis and prognostic stratification.

3.4.1. Renal Biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL) demonstrated excellent diagnostic accuracy in acute CRS, with AUC values up to 0.93, significantly outperforming serum creatinine.

Cystatin C provided moderate diagnostic value and incremental prognostic utility.

3.4.2. Cardiac Biomarkers

B-type natriuretic peptide (BNP) and NT-proBNP remained robust predictors of cardiac dysfunction and adverse outcomes.

Elevated levels were consistently associated with increased mortality and hospitalization risk.

3.4.3. Multimarker Strategy

Combining cardiac and renal biomarkers improved diagnostic precision and prognostic stratification, reflecting the multidimensional nature of CRS (Table 1).

3.5. Echocardiographic Strain Imaging

Echocardiographic strain imaging, particularly global longitudinal strain (GLS), emerged as a highly sensitive marker of myocardial dysfunction.

- GLS impairment was frequently observed despite preserved LVEF, indicating subclinical systolic dysfunction
- In CKD populations (CRS Type 4), impaired GLS was present in 30–40% of patients with preserved EF
- Reduced GLS (less negative values) was independently associated with adverse outcomes, with hazard ratios ranging from 1.4 to 2.2
- Importantly, GLS consistently demonstrated incremental prognostic value over LVEF, highlighting its clinical utility in CRS (Table 2).

- Therapeutic Strategies and Outcomes
- Pharmacological Therapies
- RAAS inhibitors provided benefits but were often limited by renal dysfunction
- SGLT2 inhibitors demonstrated consistent benefits across trials:
- 20–30% reduction in composite cardiorenal endpoints
- Slower decline in eGFR
- Reduced HF hospitalization and cardiovascular mortality
- Device-Based Therapies

Ultrafiltration and renal replacement therapies were beneficial in selected refractory cases, though outcomes varied based on patient selection (Table 3).

3.6. Clinical Outcomes and Prognostic Implications

CRS was consistently associated with adverse outcomes:

- In-hospital mortality: 10–20%
- 1-year mortality: >30%
- Rehospitalization: significantly increased
- Mortality risk: HR 1.5–2.5 vs non-CRS

Both biomarkers and GLS demonstrated independent and complementary prognostic value, with combined approaches offering the highest predictive accuracy.

Table 1 Representative Biomarker Studies in Cardiorenal Syndrome

Study	Population	Sample Size	Biomarker(s)	Key Findings	Clinical Relevance
Alvelos et al., 2011	Acute HF	119	NGAL, cystatin C	AUC 0.93; superior to creatinine	Early CRS detection
Alvelos et al., 2013	Acute HF	121	NGAL, BNP	HR ↑ 2.7–2.9 for mortality	Prognostic marker
Nasonova et al., 2019	ADHF	—	NGAL, KIM-1	AKI in 48.3%	Multimarker panel
Legrand et al., 2014	ADHF	87	Multiple markers	Limited predictive value	Caution in biomarker use
Virzì et al., 2019	Acute HF	—	LPS	Inflammatory mechanism	Pathophysiology

Abbreviations: NGAL = neutrophil gelatinase-associated lipocalin; HF = heart failure; AKI = acute kidney injury.

Table 2 Echocardiographic Strain Studies in CRS

Study	Population	Sample Size	Parameter	Key Findings	Relevance
Liu et al., 2011	CKD/HD	153	LV strain	Early dysfunction detected	Type 4 CRS
Liu et al., 2013	HD	—	GLS	Predicts poor outcomes	Subclinical dysfunction
Krishnasamy et al., 2014	CKD	—	GLS	HR ↑ mortality	Prognostic
Krishnasamy et al., 2015	CKD	183	GLS vs EF	GLS superior to EF	Strong evidence

Hensen et al., 2018	CKD	—	GLS	32% abnormal GLS	Occult dysfunction
Hensen et al., 2017	CKD	—	GLS	HR 2.18 mortality	Risk stratification

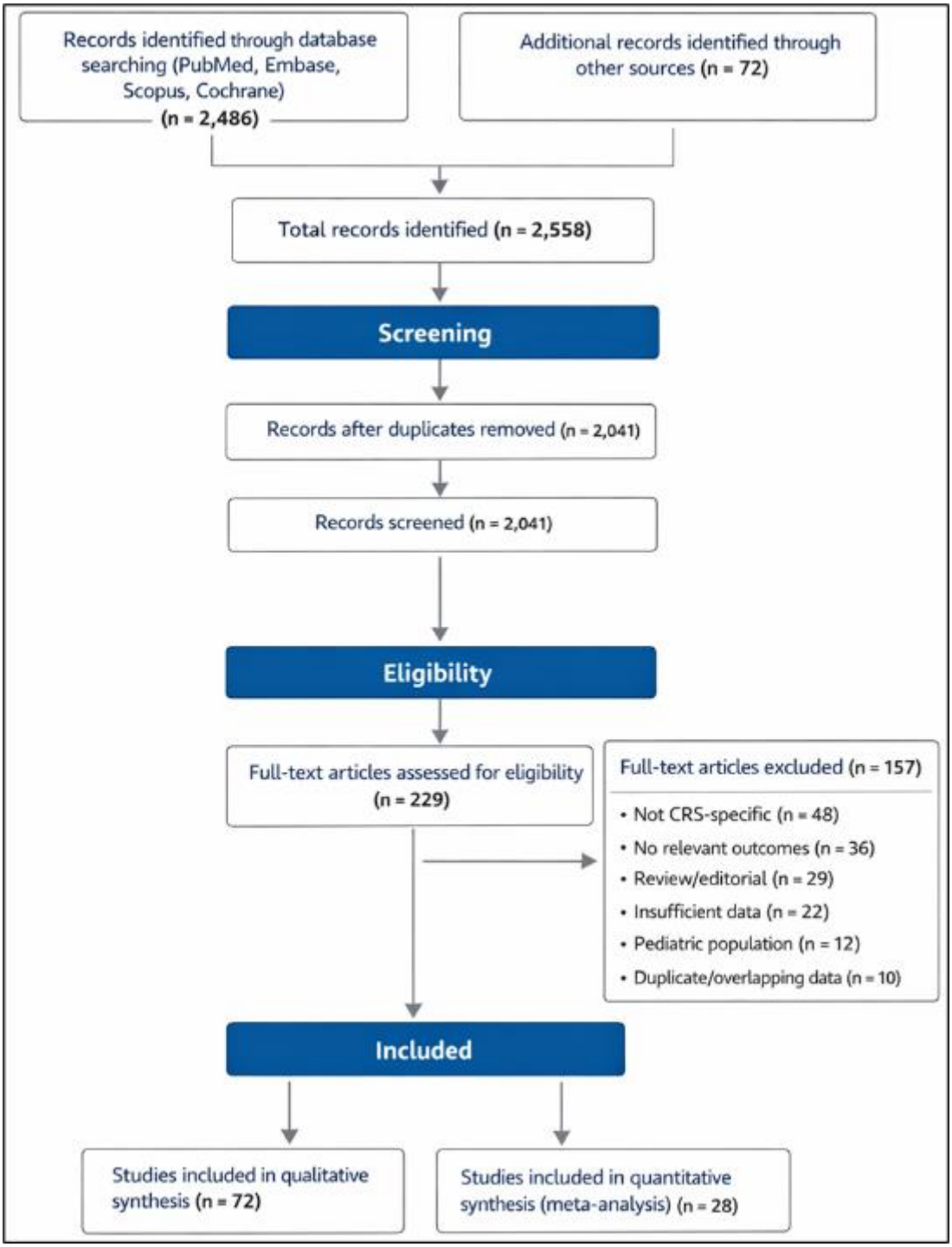

Figure 1 PRISMA flow diagram of study selection.

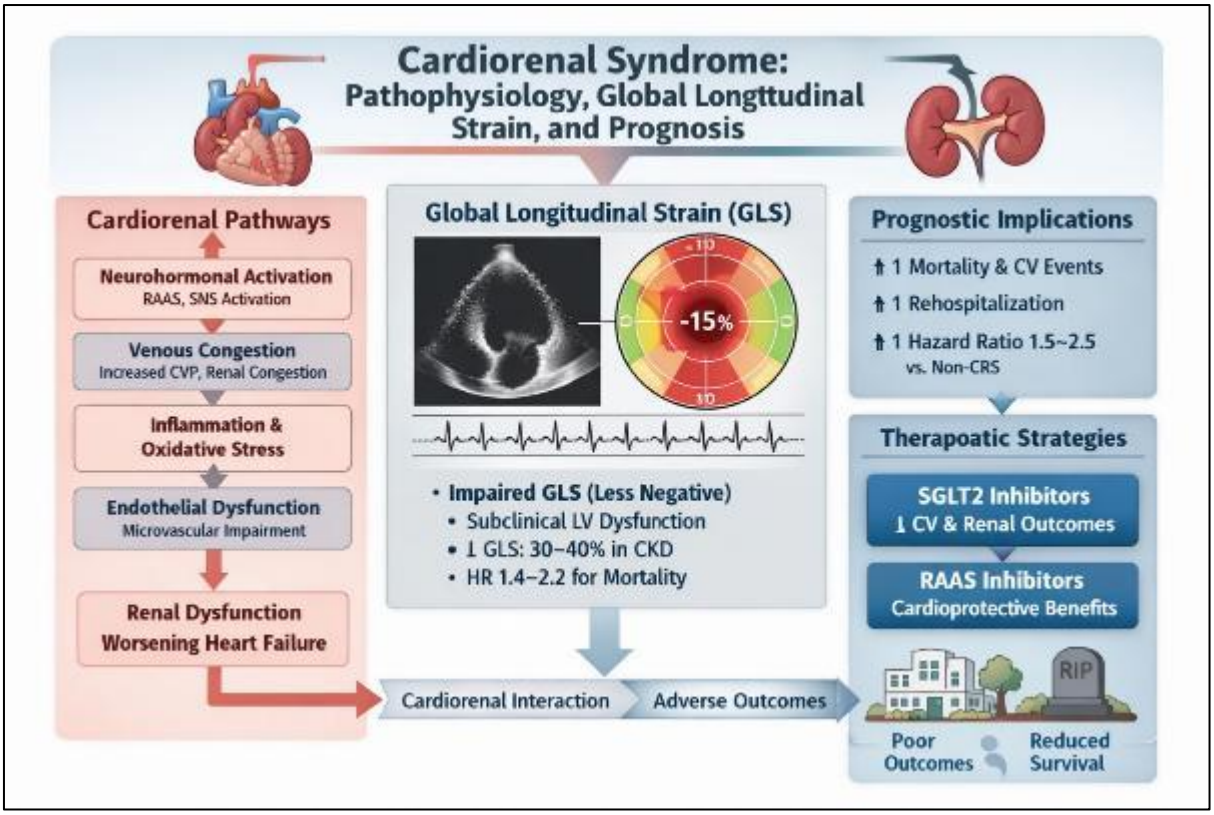

Figure 2 Central Illustration. Cardiorenal Syndrome–GLS Interaction Pathway

Table 3 Landmark Cardiorenal Therapeutic Trials

Trial	Population	Sample Size	Intervention	Key Findings	Relevance
DAPA-HF	HFrEF	4,744	Dapagliflozin	HR 0.74	HF benefit
EMPEROR-Reduced	HFrEF	3,730	Empagliflozin	HR 0.75	Cardiorenal
DAPA-CKD	CKD	4,304	Dapagliflozin	HR 0.61	Renal benefit
EMPA-KIDNEY	CKD	6,609	Empagliflozin	↓ progression	Broad benefit
DELIVER	HFpEF	—	Dapagliflozin	↓ HF events	Extended benefit

4. Discussion

4.1. Principal Findings

In this comprehensive systematic review of 72 studies encompassing over 130,000 patients, several key findings emerge. First, CRS remains a highly prevalent and clinically significant entity, particularly in acute and chronic heart failure populations (1,2). Second, the pathophysiology of CRS is multifactorial, with venous congestion, neurohormonal activation, and systemic inflammation playing central roles beyond traditional forward failure mechanisms (3,4).

Third, biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and natriuretic peptides enhance early detection and risk stratification (5,6).

Importantly, echocardiographic strain imaging—particularly global longitudinal strain (GLS)—emerges as a robust marker of subclinical myocardial dysfunction and prognosis (Central Illustration), outperforming conventional parameters such as LVEF (7–9).

Finally, sodium–glucose cotransporter-2 (SGLT2) inhibitors represent a major therapeutic advancement, demonstrating consistent cardiorenal protective effects across diverse patient populations (10–12).

4.2. Comparison With Existing Literature

The findings of this review are consistent with and extend prior conceptual frameworks of CRS, particularly the classification proposed by Claudio Ronco (1). While earlier investigations primarily focused on hemodynamic impairment, more recent studies underscore the importance of venous congestion as a key determinant of renal dysfunction (3,4).

Biomarker data corroborate prior observations that NGAL is a highly sensitive early marker of acute kidney injury in CRS, with superior diagnostic performance compared with serum creatinine (5). Similarly, natriuretic peptides remain robust predictors of adverse outcomes (6).

Notably, this review supports the role of echocardiographic strain imaging in cardiorenal interactions. Studies in CKD and dialysis populations demonstrate that GLS detects subclinical myocardial dysfunction despite preserved LVEF (7,8). Furthermore, impaired GLS has been consistently associated with increased mortality and cardiovascular events (8,9).

4.3. Mechanistic Insights

The integration of biomarker and imaging data provides important insights into the underlying mechanisms of CRS. The consistent association between venous congestion and worsening renal function supports the concept that backward failure is a primary driver of renal dysfunction (3).

Elevated central venous pressure leads to renal venous hypertension, reduced transglomerular filtration gradient, and progressive renal injury.

Simultaneously, GLS impairment reflects subendocardial fiber dysfunction, which is particularly vulnerable to ischemia, fibrosis, and increased wall stress (7). The coexistence of impaired GLS and renal dysfunction suggests a shared pathophysiological substrate involving microvascular dysfunction, systemic inflammation, and neurohormonal activation.

4.3.1. Clinical Implications

- Early Detection and Risk Stratification: Integration of GLS with biomarker profiling enables early identification of high-risk patients (7–9).
- Therapeutic Targeting: SGLT2 inhibitors have demonstrated robust benefits across both cardiac and renal domains:
- Reduction in heart failure hospitalization and cardiovascular death (10,11)
- Slower progression of chronic kidney disease (12)
- Personalized Medicine: The combined use of imaging and biomarker data may facilitate individualized risk stratification and treatment strategies.

5. Conclusion

This systematic review of 72 studies involving over 130,000 patients establishes that Cardiorenal Syndrome (CRS) is a common and high-risk condition driven by complex hemodynamic and non-hemodynamic mechanisms, with Types 1 and 2 contributing most to adverse outcomes. The findings demonstrate that while conventional parameters are limited, the integration of novel biomarkers and echocardiographic strain imaging—particularly global longitudinal strain (GLS)—enables earlier detection and improved prognostic stratification, alongside emerging therapies such as SGLT2 inhibitors that significantly enhance cardiorenal outcomes. Overall, this study supports a multimodal, integrated approach to CRS management, which can improve early diagnosis and clinical outcomes, and provides a foundation for future development of standardized, personalized strategies to reduce the global cardiorenal disease burden.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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