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BIOMARKERS AND THERAPEUTIC INTERVENTIONS FOR CARDIORENAL SYNDROME: A LITERATURE REVIEW

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ABSTRACT

Acute or chronic cardiac and renal failure interact to worsen both organs' states in cardiorenal syndrome (CRS), a complicated medical disorder. This review covers biomarkers and therapeutic strategies in CRS management, highlighting current advancements and future prospects. A Scopus, Google Scholar, and PubMed search technique was used to examine relevant material from 2019-2024. Troponin and NT-proBNP are important cardiac biomarkers for CRS severity assessment, disease progression, and therapy options. Serum creatinine, cystatin C, and NGAL also reveal renal function and prognosis. In CRS, albuminuria, a measure of renal function and chronic kidney disease severity, is related to poor outcomes.Diuretics and ultrafiltration reduce fluid excess in CRS, while RAAS inhibitors increase survival and reverse cardiac remodeling in heart failure patients. SGLT2 inhibitors may protect the kidneys and heart. In certain cardiac diseases, non-pharmacological methods like ICDs and CRT may help. This review concludes with advancements in CRS biomarkers and treatment. Cardiac and renal biomarkers can predict CRS and SGLT2 inhibitors may improve CRS therapy. Research is required to improve these therapies and investigate other therapeutic ways to improve patient outcomes.

INTRODUCTION

The combination of acute or chronic cardiac and kidney disease, which sets off a series of feedback processes that harm both organs, is known as cardiorenal syndrome (CRS) [(1)]. A close association between the kidney and the heart with distinct bidirectional and dynamic pathways—including

hemodynamic interactions in heart failure (HF)—was shown by clinical and epidemiological research [(2)]. Kidney disease may exacerbate cardiovascular dysfunction by impacting the heart and circulatory system; in turn, cardiovascular impairment can deteriorate kidney function via a variety of pathways

that affect the kidneys [3]. As a result, individuals with chronic kidney disease (CKD) often also have cardiovascular disease (CVD), and vice versa.

The onset and progression of cardiac and renal illnesses have been linked to hemodynamic changes, neurohormonal dysregulation, inflammatory activation, fibrosis, endothelial dysfunction, and atherosclerosis. These factors create a vicious cycle that damages both organs in turn [4]. This suggests a shared mechanism for the kidneys' and heart's interaction, which results in the decrease of both organ systems in CRS.

A decline in renal function has been seen in over 20% of hospitalized patients with acute heart failure (HF), whereas more than 50% of patients with chronic heart failure had chronic kidney disease (CKD) [5]. In a similar vein, almost 50% of CKD patients had a 20-fold higher risk of CVD [6]. Acute kidney failure (AKI) varied from 23% to 35% in several additional publications, which included patients with both acute and chronic heart failure (HF) [7]. The prevalence of CKD was estimated to be about 50% and 40%, respectively. When CVD and renal illness coexist, the prognoses of both conditions deteriorate: hospital stays last an average of two to four days longer, and there is a higher chance of death and rehospitalization throughout the six- to four-year follow-up period. Since the combination of both cardiac and renal dysfunction may worsen the prognosis in these patients, identifying those with CRS has a significant impact on prognosis. It is true that CRS, especially type 1 CRS, is associated with a high death rate as well as a high in-hospital mortality rate [8].

HF and renal structural and functional abnormalities are needed for CRS. Biomarkers predict heart failure and renal disease by assessing cardiac dysfunction and renal impairment. Biomarkers may aid CRS diagnosis, etiology, and therapy [9]. CRS pathophysiological advances have found biomarkers that may improve diagnosis and therapy. CRS patients are not adequately identified or included in HF and CKD research; therefore, landmark trials provide therapy options. Although CRS is a separate condition with significant morbidity and mortality, research is still ongoing to understand the etiology and management of acute and chronic CRS subtypes. The best CRS treatment needs more focused study to enhance prognosis and minimize mortality.

It is important to highlight that juvenile CRS types, which differ from adult CRS types in some ways, are also presently being defined. Less is known about the prognosis, risk factors, and prevalence of pediatric CRS. A recent study has provided a thorough overview of pediatric CRS [10]. The pathogenesis of CRS in adults, the use of biomarkers in cardiac and renal failure, and prospective discoveries on new treatments for the treatment of CRS patients will all be covered in this review article.

METHODOLOGY

This comprehensive review used an integrated strategy to methodically collect and assess pertinent material from reliable academic sources, such as PubMed, Scopus, and Google Scholar. To guarantee a comprehensive study, standard procedures from earlier systematic reviews were modified due to the intricacy of the subject matter pertaining to biomarkers and treatment strategies for cardiorenal syndrome (CRS). Search terms including "renal biomarkers," "cardiorenal syndrome," "biomarkers," "therapeutic interventions," and "cardiac biomarkers" were used to find relevant research.

Inclusion and Exclusion Criteria:

Articles on CRS treatment strategies and biomarkers were deemed suitable for inclusion in this review. To reflect current advancements in the area, we only considered papers that were published in English over the previous five years (2019–2024). Studies with human subjects that contributed significantly to our understanding of the workings, developments, and clinical uses of biomarkers and CRS treatment approaches were included. Studies that didn't directly address the subject or didn't follow acceptable

methodology, on the other hand, weren't included. Every discovered article was carefully examined to determine its applicability and appropriateness for inclusion using abstracts and titles.

Categorization and Analysis:

The vast diversity of literature on biomarkers and treatment strategies for CRS was arranged and analyzed using a systematic categorization technique. This review's main goals were to clarify the function of biomarkers in the pathophysiology of CRS and assess how well treatment measures may slow the course of the illness. Several different aspects were investigated through the creation of analytical categories, such as diuretic therapy, renin-angiotensin system inhibitors, and sodium-glucose cotransporter-2 inhibitors (SGLT2i), in addition to cardiac and renal biomarkers (e.g., creatinine, cystatin C). The focus was on clarifying the underlying processes, clinical efficacy, and possible synergies between various therapy modalities. With the help of these topics and the literature, this review attempts to provide a thorough picture of the state of biomarkers and treatment approaches for CRS today.

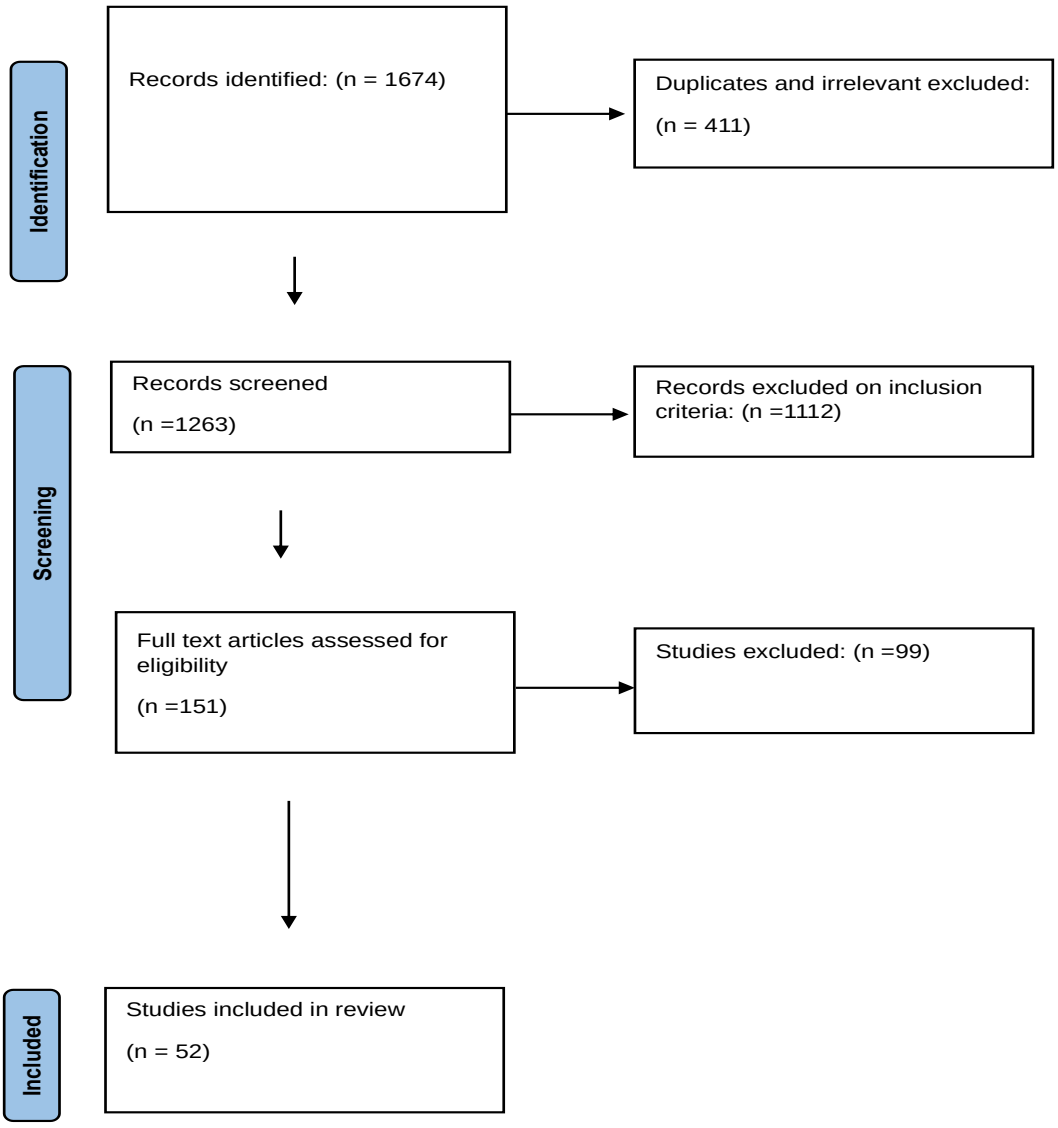

FIGURE 1 *(PRISMA FLOW DIAGRAM)*

RESULTS

Biomarkers in Cardiorenal Syndrome:

Cardiac Biomarkers:

Troponin:

Troponins control cardiac and skeletal muscle contraction. Troponin contains C, T, and I isoforms. Troponin C is present in skeletal and cardiac muscle, unlike troponin T and I, which are cardiac muscle-specific and good indicators of myocardial damage. An immunobiological study links serum troponin to myocardial damage [11]. Even without cardiac damage, CKD elevates troponin levels. Subclinical damage such uremic toxicity or hypertensive cardiac disease lowers serum troponin clearance and increases cardiomyocyte troponin release [12].

To evaluate the validity of the traditional upper reference limits (URLs) for hsTnT in CKD patients, recent retrospective research on participants in the Chronic Renal Insufficiency Cohort (CRIC) examined the serum high sensitivity troponin T (hsTnT) concentrations of ambulatory CKD patients. The researchers discovered that 43% of the 2312 CKD patients had a resting hsTnT concentration higher than the recommended URL. Patients with severe renal failure (CKD grade IV, eGFR < 30 mL/min/1.73m2) showed even greater evidence of this result, with 68% of them having a resting hsTnT concentration over the recommended URL. A model derived from further data analysis showed that for every 15 mL/min/1.73 m2 drop in eGFR in patients with CKD, the threshold for the 99th percentile of blood hsTnT concentrations rises by 44% [13].

Similar results were found in another research that looked at the predictive significance of high sensitivity troponin I (hsTnI) blood concentrations in individuals with chronic kidney disease (CKD). At 1-year follow-up, patients with CKD and hsTnI concentrations above the 99th percentile had a significantly higher risk of myocardial infarction or cardiac death compared to patients with elevated hsTnI concentrations and preserved renal function (24% vs. 10%, HR = 2.19, 95%CI 1.54-3.11), even though the diagnostic accuracy of hsTnI concentrations was lower in CKD patients compared to patients with preserved renal function (positive predictive value 50% vs. 63%, specificity 71% vs. 92%) [14]. There is evidence that the diagnostic accuracy of hsTnT concentrations for acute myocardial injury in patients with chronic kidney disease (CKD) can be significantly improved with a few modifications. Alushi et al. found that the specificity increased from 10% to 65% when they used hsTnT cut-offs four times greater than the conventional ones, but the sensitivity decreased from 98% to 83%. By creating a model that included the baseline hsTnT concentration with an absolute change in hsTnT concentration three hours after the index measurement, this was lessened. With 98% sensitivity, 55% specificity, 93% positive predictive value, and 86% negative predictive value, this model produced better diagnostic accuracy [15].

Troponin's prognostic usefulness for CRS is controversial and limited. Ledwoch et al. discovered that hsTnT had a significantly lower predictive accuracy for 30-day mortality in patients with acute heart failure and impaired renal function (defined as eGFR < 45 mL/min/1.73m2) than in patients with acute

heart failure and preserved renal function (AUC 0.63 vs. 0.74, P = 0.049) [16]. He and colleagues assessed how well cardiac troponin I (cTnI) predicted the onset of type I CRS in individuals suffering from acute myocardial infarction. The AUC of cTnI was 0.76; however, in a statistical model, the AUC increased to 0.92 when cTnI was coupled with NT-proBNP, baseline eGFR, and white blood cell count. This suggests that other biomarkers may enhance and augment the predictive and diagnostic utility of cTnI for CRS when combined [17].

N-terminal pro-brain natriuretic peptide:

In response to ventricular stretching from increased circulation volume, cardiomyocytes generate N-terminal pro-brain natriuretic peptide. The volume overload proxy NT-proBNP has been extensively studied in acute cardiac failure, renal damage, and CRS. N-terminal pro-brain natriuretic peptide may predict renal function deterioration and fluid overload in acute heart failure patients. After reviewing EVEREST trial data, McCallum et al. discovered that patients with increased serum NT-proBNP and heart failure with reduced ejection fraction (HFrEF) were more likely to have a >40% eGFR drop (HR = 2.62, 95%CI 1.62-4.23) [18]. McCallum et al. examined DOSE and CARRESS trial data separately. In acute decompensated heart failure patients, NT-proBNP drop was substantially related with a reduced risk of mortality or rehospitalization, although eGFR was not. If NT-proBNP dropped along with eGFR, mortality and rehospitalization risk reduced.

Using renal function as a basis, De la Espriella et al. assessed the prognostic value of NT-proBNP in patients with acute heart failure. They discovered that, although serum NT-proBNP concentration in this patient group was positively and linearly associated with mortality, its predictive value significantly decreased in patients with eGFR < 45 mL/min/1.73m2 [19]. Researchers Zhao et al. looked examined the predictive efficacy of urinary NT-proBNP (uNT-proBNP) for the development of type I CRS in patients with acute decompensated heart failure. N-terminal pro-brain natriuretic peptide has also been studied as a urine biomarker. With an AUC of 0.93 (95%CI 0.87-0.97), they discovered that uNT-proBNP was a substantial and trustworthy predictor of the development of type I CRS [20].

The results of the studies mentioned in this paragraph suggest that although NT-proBNP can be used to guide pharmacologic therapy, its greatest value is in its ability to diagnose CRS with a reasonable degree of accuracy, particularly when paired with indicators of renal function and inflammation. NT-proBNP is a much more dependable measure of the efficacy of diuretic treatment than eGFR, as shown by McCallum et al, [21]. Moreover, early treatment termination or de-escalation owing to perceived (falsely) worsening renal function would result from depending only on eGFR for the titration of diuretic therapy in fluid-overloaded CRS patients. NT-proBNP readings and clinical findings (physical examination and ultrasonography) should instead guide and steer diuretic treatment since NT-proBNP is the sole accurate predictor of unfavorable short- and long-term outcomes in this patient group.

Renal Biomarkers:

Creatinine:

Serum creatinine, the most frequent renal function indicator, reflects acute and chronic kidney disease. Creatine metabolism ends. Glomerular filtration eliminates creatinine due to its low molecular weight and albumin non-binding. Proximal renal tubule secretion blockers increase creatinine, suggesting

activity. CKD proximal tubular secretion increases creatinine elimination when glomerular filtration decreases. CKD patients' serum creatinine or creatinine clearance may overestimate GFR. Blood creatinine concentrations are unsatisfactory renal function markers in acute kidney injury because vigorous intravenous fluid resuscitation dilutes or increases them [22]. Calculating GFR from serum creatinine alone is problematic. When the value obtained in the emergency department (ED) was compared to either their baseline or the repeat value measured six to twenty-four hours after admission to the hospital ward, nearly one-third of the patients had a significant change (> 15% increase or > 18% decrease) in the measured serum creatinine [23].

Neutrophil gelatinase-associated lipocalin (NGAL) serum concentrations and serum creatinine concentration values measured on the first day of hospitalization, for instance, were combined in a nomogram that showed significantly higher diagnostic accuracy (area-under-the-curve, or AUC) of 0.79 for predicting the development of type I CRS than serum creatinine alone [24]. Although there are several drawbacks to using creatinine as the primary biomarker of renal function and tissue integrity, it is important to remember that formulas such as the CKD Epidemiology Collaboration (CKD-EPI) formula and the Modification of Diet in Renal Disease (MDRD) formula, which are the most commonly used to estimate GFR, depend on the serum creatinine concentration as a necessary component of their calculations. The 2009 CKD-EPI formula is advised to be used for estimating GFR, according to a recent position statement from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). However, there is rising recognition for cystatin C-based formulae [25].

Cystatin C:

A significant marker in CRS, cyclostatin C has been investigated as a renal and cardiac outcome prognosticator. Patients with elevated serum cystatin C concentrations have a higher risk of all-cause mortality (hazard ratio (HR) = 2.33; 95% confidence interval (CI): 1.67-3.27, P < 0.001), according to the results of a meta-analysis of studies using cystatin C as a prognostic marker in patients with acute heart failure [26]. Subgroup analysis of the included studies revealed the elevated risk, which was consistent irrespective of the kind of heart failure (acute vs chronic), research sample size, or cystatin C cut-off value. To predict a composite outcome of in-hospital mortality, the need for renal replacement therapy, or severe right ventricular outcome in patients with a recently implanted left ventricular assist device (LVAD) due to advanced heart failure, Pinsino et al. compared the accuracy of eGFR estimated with creatinine to eGFR estimated with cystatin C [27]. The researchers discovered a strong correlation between the composite outcome and eGFR as measured by cystatin C (odds ratio (OR) 1.16, 95%CI 1.02-1.31; for every 5 mL/min/1.72 m2 reduction in eGFR). When eGFR was calculated using creatinine, there was no discernible relationship with the main outcome. Increased blood cystatin C concentrations relative to baseline were shown to be strongly linked with the incidence of new-onset cardiovascular disease (defined as newly diagnosed heart disease, stroke, or both) in a longitudinal Chinese research including over 7000 patients [28].

Neutrophil gelatinase-associated lipocalin:

NGAL, also known as neutrophil gelatinase-associated lipocalin, belongs to the lipocalin family of proteins, which are primarily involved in molecular transport inside the human body [29]. It is a marker of acute renal tubular damage and necrosis because it is progressively produced and expressed on the

cells of the proximal and distal renal tubules after acute ischemia [30]. It has been studied as a potential diagnostic and prognostic factor for CRS and acute renal damage. Song et al. investigated the relationship between serum NGAL levels and type I CRS. They discovered that elevated blood NGAL concentrations, with an AUC of 0.88 (95%CI 0.81-0.94), 95% sensitivity, and 81% specificity, were a sufficient diagnostic tool for type I CRS. The AUC was 0.92 (95%CI 0.87-0.96) with 80% specificity and 93% sensitivity when paired with NT-proBNP [31].

However, serum NGAL had an AUC of only 0.45 (95%CI 0.36-0.54) in a retrospective investigation of individuals with type I CRS by Ferrari et al., and its content was not substantially linked to the likelihood of developing CRS. The authors speculate that the group under study had low-grade heart failure and relatively minor renal impairment, which might have skewed the results [32]. The predictive efficacy of NGAL for the development of AKI in patients with acute heart failure has been examined in several research. Another research by Nasonova et al. found that urine NGAL had an 83% sensitivity and an AUC of 0.83 when used to predict acute decompensated heart failure in individuals [33].

Albuminuria:

Albuminuria has historically indicated renal function. Chronic kidney disease was rated 1–5 by 2012 KDIGO. Grade 3 included eGFR a and b subgrades and albumin/creatinine ratio stages [34]. Large population studies relate albuminuria to end-stage renal disease, cardiovascular disease, and all-cause mortality, making it critical for grading chronic kidney disease (CKD) severity (Matsushita et al., 2010).

Recent in vitro research utilizing human kidney cells and a type I CRS model has shown that albumin damages renal tubules in a dose-dependent manner, suggesting that it is a pathophysiological component that exacerbates AKI in experimental settings [35]. Researchers have looked at albuminuria as a disease prediction sign for both acute and chronic heart failure. In contrast to healthy controls, patients with CKD had a prevalence of left ventricular hypertrophy (LVH) on echocardiography that was more than four times higher, and there was a significant independent relationship between LVH and albuminuria (P = 0.002), according to a study on cardiac morphology in CKD patients by Landler et al [36]. Wang et al. studied 1818 patients with acute decompensated heart failure and found that even after controlling for other significant clinical factors (age, history of arterial hypertension, presence of atrial fibrillation/flutter, New York Heart Association (NYHA) class, heart rate, systolic blood pressure, body mass index (BMI), hemoglobin, serum albumin, serum creatinine, eGFR, N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular diastolic dysfunction, left ventricular ejection fraction (LVEF), and prescription of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers or diuretics) (HR = The probability of the mentioned adverse events increased as the degree of albuminuria increased (P = 0.004) [37]. Increased serum albumin concentrations were significantly associated with a lower risk of death or hospitalization due to heart failure (HR = 0.78, 95% CI 0.69-0.90, P < 0.001) after adjusting for baseline albumin concentrations, anemia, age, eGFR, BMI, NYHA, and history of diabetes mellitus, according to research by Kato et al. on the relationship between serum albumin concentrations and 1-year adverse outcomes in acute decompensated heart failure patients [38]. According to research by Alatas et al., microalbuminuria was not a predictor of in-hospital mortality in patients with intact ejection fraction, but it was in patients with acute heart failure and limited and mid-range ejection fractions [38].

Therapeutic Strategies in CRS:

Diuretic and Ultrafiltration Therapy:

Central and peripheral congestion are often seen in individuals with acute or chronic HF, and diuretics are a valuable treatment option with or without CRS. Diuretics do, however, not reduce HF hospitalizations or death, even if they do relieve symptoms. The preferred diuretics for either acute or chronic heart failure are loop diuretics, which include furosemide, bumetanide, torsemide, and ethacrynic acid [39]. Acetazolamide increases the diuretic efficiency in terms of effective decongestion in patients with acute decompensated HF. Despite being well tolerated, acetazolamide medication had no impact on mortality, renal function, or hypokalemia in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) study [40]. Diuretic synergy may be helpful in some situations for individuals with acute heart failure, however, it is unclear whether this idea would apply to CRS as well. Diuretics may decrease renal function, especially in individuals with severe heart failure [39].

The braking phenomenon, which includes long-term induction of distal tubular hypertrophy and decreasing diuretic effectiveness with each subsequent dosage, may be brought on by the administration of diuretics [39]. The braking phenomena may be lessened by sodium replacement. It has been suggested that increased distal salt transport might reduce furosemide's maximum effectiveness. The effectiveness of certain diuretics may be increased when used in combination. The combination use of thiazide-type diuretics has been proposed to potentially enhance the sodium excretion generated by furosemide [41].

Using a negative transmembrane pressure gradient and whole venous blood, ultrafiltration (UF), also known as aquapheresis, is the process of directly removing isotonic fluid from the body by pumping the blood over a semipermeable membrane. It has been promoted as a way to enhance decongestion in patients with DR or as a substitute for harsh IV diuretic regimens in congested AHF patients (1) [42] [43] [44] [45]. In addition, it has the potential to reduce electrolyte loss and remove more salt from the body than loop diuretics while avoiding the neurohormonal activation linked to long-term and/or recurrent diuretic dosage.32, 34 UF may be started outside of the critical care unit and is accomplished via central or peripheral venous access. Clinicians should think about using UF sparingly while they wait for the results of future outcomes studies. Several clinical trials comparing UF to different diuretic regimens have been carried out, and the results have produced somewhat disparate conclusions regarding the clinical value of UF over diuretic protocols and the impact of UF on renal function (1) [42] [43] [44] [45]. Furthermore< ultrafiltration therapy did not result in a decline in renal function in individuals with acute heart failure [46].

Renin Angiotensin System Inhibitors:

In heart failure (HF) clinical trials, neuro-hormonal modulation may enhance survival, reverse cardiac remodeling, and lessen symptoms. Modern HF therapy relies on neuro-hormonal drugs [47]. Type 2 CRS causes neurohormonal dysregulation, including RAAS hyperactivity, oxidative stress, inflammation, and vascular remodeling. Agents that interact with these systems may treat this [48]. MRA with RAAS inhibitors like ACEI, ARB, or ARNI enhances HF prognosis and renal function. CRS patients should not

use RAAS inhibitors, even if current data suggests they are safe in advanced CKD patients and may prevent pathological hyperfiltration by improving intrarenal hemodynamics [49]. However, controversial findings, primarily from small observational studies, have raised concerns about the use of RAAS inhibitors. Research suggests that RAAS inhibitors may reduce GFR more quickly in CKD patients and jeopardize their remaining renal function [50]. ACEi do not, however, stop the GFR reduction in HFrEF [51]. Benefits for both acute and chronic heart failure outcomes have been shown by ARNI [52]. In patients with eGFR < 30 mL/min, data are sparse, however ARNI may retain renal function more efficiently than ACEi and ARB by slowing the steady reduction of GFR associated with HF [53] [54]. Despite the possibility that RAAS inhibitors, such as ARNI, might be used for other concurrent indications including heart failure, doctors often hesitate to prescribe these drugs to patients with advanced chronic kidney disease (CKD) because of these contradictory data. This may commonly result in these therapies being stopped altogether or in their doses being reduced.

SGLT2 Inhibitors:

Early clinical studies, like DECLARE-TIMI, have shown the effectiveness of SGLT2i in lowering cardiovascular mortality and HF hospitalizations in diabetic patients with HFrEF. SGLT2i was first utilized as an anti-diabetic medication [55]. SGLT2i in particular demonstrated improved cardiovascular and renal outcomes in these early trials intended for patients with type 2 diabetes mellitus (T2DM), such as a decrease in cardiovascular death, nonfatal MI, nonfatal stroke, hospitalizations for heart failure, and worsening of nephropathy (progression to macroalbuminuria, doubling of serum creatinine, ESRD, or death for renal disease).

Independent of diabetes and concurrent CKD, further research showed that individuals treated with SGLT2i had a smaller yearly decrease in renal function and a reduction in HF hospitalizations and CV mortality in a sample of HF patients with reduced and maintained EF [56] [57] [58]. Furthermore, independent of the existence of diabetes, current data supports the effectiveness of SGLT2i in terms of nephroprotection by lowering the deterioration in renal function and CV mortality in patients with CKD [59]. A meta-analysis showed that SGLT2i had a protective effect in acute renal failure as well, primarily because this medication class may enhance tubulointerstitial hypoxia, preserve tubular cell integrity, and avoid proteinuria [60]. These clinical characteristics suggest that SGLT2i may be a useful therapeutic option for the management of CRS.

In addition to their potent diuretic and metabolic effects, SGLT2is may also modulate neurohormones and lessen oxidative stress, inflammation, and cardiovascular remodeling [61]. The nephroprotective impact of this family of medications has been shown in both experimental and clinical investigations to be good, even greater than that of ACEi or ARBs, which are thought to be the most effective treatments for maintaining kidney function in patients with heart failure [62] [63]. Through the inhibition of Na+/glucose cotransporter 2, SGLT2i lowers intravascular volume, improves glycemic control, and lowers intraglomerular pressure by contrasting tubuloglomerular feedback, ultimately protecting the glomerular endothelium [64]. By reducing glucose and salt reabsorption, SGLT2i therapy preserves sodium supply to the macula densa and improves hemodynamic effects (59). Therefore, during the early stages of therapy, SGLT2i may induce natriuresis, which might trigger systemic RAAS. However, chronic SGLT2i treatment does not seem to impact RAAS activity [65]. Moreover, it has been shown that

SGLT2i therapy decreases hyperfiltration by raising the amounts of prostaglandin and adenosine in the urine without raising the renal vascular tone [66].

Non-Pharmacological Approaches:

While controversial, non-pharmacological therapy may enhance cardiorenal function and mortality in HF and CKD patients. Studies show that implantable cardiac defibrillators (ICDs) may aid CRS patients as well as HF patients. For patients who have recovered from ventricular arrhythmia linked to hemodynamic instability and have HF symptoms and an LVEF < 35%, ICD is recommended to reduce the risk of sudden death and all-cause mortality, even after receiving optimal medical care for a minimum of three months. For ECG QRS lengths beyond 150 ms, cardiac resynchronization therapy (CRT) is recommended [67]. This is especially true if a left bundle branch block is present. The usage of device treatment is anticipated to be relatively low in this patient group (less than 10% of cases), even though the concurrent presence of HF in patients with ESRD raises the worldwide mortality prevalence by 50% [68]. The primary cause of this is the dearth of proof from randomized clinical studies. Specifically, a meta-analysis of ICD trials has shown no discernible benefit from device implantation in patients with reduced renal function who have congestive heart failure (CHF) [69]. This is even after accounting for the non-arrhythmic causes of death in these patients and the high burden of non-cardiovascular comorbidities, such as bleeding, bacteremia, vascular access, and higher rates of lead-related complications, which may lower the net benefit of ICD implantation in patients with congestive heart failure (CRS) [70].

DISCUSSION

The complicated interaction between cardiac and renal failure that exacerbates the states of both organs is known as cardiorenal syndrome (CRS). In addition to offering light on current developments in the area and possible future initiatives, the systematic review sought to clarify the function of biomarkers and treatment strategies in controlling CRS.

According to the study, cardiac biomarkers including NT-proBNP and troponin are crucial markers of ventricular stretching and myocardial injury, respectively. Even in CKD patients without obvious cardiac impairment, elevated troponin levels were found, indicating subclinical myocardial injury and altered serum clearance [13]. Similarly, while its predictive value varies depending on renal function, NT-proBNP is a reasonable predictor of fluid overload and impairment of renal function in patients with acute heart failure [19] [20].

Renal biomarkers were also emphasized as critical measures of renal function in CRS, particularly serum creatinine and cystatin C. However, because of things like fluid resuscitation effects and variability in creatinine clearance, these measures have their limits [23]. When assessing GFR, cystatin C is a more dependable option than creatinine, especially in individuals with acute heart failure [26] [27]. Another potential biomarker for CRS diagnosis and prognosis has been identified: neutrophil gelatinase-associated lipocalin (NGAL) [31].

Although the long-term advantages of diuretics are limited, therapeutic approaches in CRS generally entail diuretic and ultrafiltration therapy to address fluid excess (Felker et al., 2020). Though they may

not have a major effect on mortality or renal function, strategies like diuretic synergy with acetazolamide have shown promise in acute decompensated heart failure [40].

ARBs, ARNIs, and ACE inhibitors are examples of RAAS inhibitors, which are a mainstay of therapy for heart failure and have been studied for their potential to treat CRS. Although there are worries over the quick loss of GFR in CKD patients on RAAS inhibitors, these medications have a major positive impact on both acute and long-term heart failure outcomes [52] [49].

Due to their proven protective effects on the kidneys and heart in several clinical studies, SGLT2 inhibitors are a prospective treatment option for CRS [56] [59] l. These medications may reduce hospitalizations and enhance renal outcomes in individuals with heart failure, diabetes, and chronic kidney disease.

Patients with CRS who have certain abnormalities like ventricular arrhythmias or extended QRS intervals may benefit from non-pharmacological interventions such cardiac resynchronization therapy (CRT) and implanted cardiac defibrillators (ICDs) [67]. However, owing to the paucity of data from clinical studies, its usefulness in individuals with severe renal impairment is still up for dispute [69].

CONCLUSION

To sum up, this review offers a thorough summary of the status of research today concerning treatment strategies and biomarkers for cardiorenal syndrome (CRS). We have identified critical biomarkers that show potential for early identification and prognostication of CRS using a thorough review of the literature. These include renal biomarkers, such as creatinine and cystatin C, and cardiac biomarkers, such as troponin and NT-proBNP. Furthermore, treatment approaches such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), renin-angiotensin system inhibitors, and diuretic therapy have shown promise in controlling CRS and improving patient outcomes. To clarify the specific mechanisms of action and confirm the clinical value of these biomarkers and treatment approaches in a range of patient groups, further study is necessary.

Even though this evaluation is thorough, there are a few things to be aware of. First off, the bulk of the included studies were observational or retrospective, which restricts the capacity to demonstrate causal linkages and the applicability of results. Furthermore, variation in the patient demographics, research methods, and outcome measures across the included studies may introduce bias and compromise the validity of the results reached. Moreover, the availability and choice of the research included in this review might have been impacted by publication bias, which could distort the results as a whole. Finally, since biomarker research and treatment strategies for CRS are developing so quickly, it is necessary to continuously update and revise the material provided to maintain its relevance and currency.

Future studies should concentrate on resolving the aforementioned issues and expanding our knowledge of CRS biomarkers and therapy approaches. To verify the diagnostic and prognostic significance of discovered biomarkers and to assess the effectiveness and safety of treatment approaches in a range of patient groups, prospective, well-planned clinical studies are required. Furthermore, to create individualized treatment plans for CRS patients, integrated multidisciplinary

methods that consider the intricate interactions between cardiac and renal pathophysiology are necessary. Furthermore, there is hope for bettering the prognosis and quality of life for those with CRS via the investigation of new biomarkers and cutting-edge therapy approaches including gene and targeted immunotherapies. To solve the unmet demands and difficulties related to the treatment of CRS and to improve patient care, research in this area must be conducted going forward.

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