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Review Article

Acute Cardiorenal Syndrome: Review (Part 2)

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ABSTRACT

Recently, the definition of cardiorenal syndrome (CRS), a condition with a complicated pathogenesis, has been revised. Logically, CRS syndrome should be classified according to the initial organ that is injured, resulting in damage to another organ. Hence, there are only three main categories of CRS. Category one includes acute and chronic CRS. Category two involves renal-cardiac syndrome (RCS), which can be classified as acute or chronic. The third category represents secondary CRS, referred to as cardio-reno-cardiac syndrome (CRCS), which can be subdivided into acute and chronic CRCS. In this part of our series, we will discuss the epidemiology, pathophysiology, diagnosis, treatment, and prevention of acute CRS. We retrieved articles published on acute CRS using different keywords and phrases between January 2019 and June 2025 to achieve these goals.

Key words: Acute cardiorenal syndrome, type 1 cardiorenal syndrome pathophysiology, type 1CRS epidemiology, pathophysiology, CRS therapy and prevention

INTRODUCTION

The heart and kidneys interact via hemodynamic and nonhemodynamic pathophysiological mechanisms for cardiovascular and renal homeostasis. Cardiorenal syndrome (CRS) is a dysfunctional heart-kidney crosstalk. [1] Multifactorial bidirectional overlap of kidney and cardiac illnesses induced by one damaged main organ. [2] In 2004, the National Heart, Lung, and Blood Institute defined CRS as "the result of interactions between the kidneys and other circulatory compartments that increase circulating volume, exacerbating symptoms of HF and disease progression." [3,4] Others define acute cardiorenal syndrome (aCRS) as a condition that suddenly affects the heart, leading to acute kidney injury (AKI) due to acute decompensated heart failure (ADHF). [5] The precise importance of the decline in renal function during ADHF is currently a subject of ongoing dispute.

In the 2008 Acute Dialysis Quality Initiative (ADQI) agreement, Ronco et al. broadly divided CRS into five subgroups depending on primary organ failure and acute or chronic occurrences.

[3] The fast escalation of AKI or dysfunction in acute heart failure (AHF) is termed aCRS. aCRS is a syndrome caused by AHF that induces AKI. On the other hand, chronic CRS (cCRS) (Type 3 CRS) represents the chronic HF that causes chronic kidney disease (CKD) or end-stage renal disease (ESRD). In contrast, when the kidney is the initial organ failure site, renocardiac syndrome (RCS) is CRS's exact and most representative nomenclature.

The third type (previously known as type 5 or secondary CRS) is cardio-reno-cardic syndrome (CRCS), which can be subdivided into acute and chronic (A—and CCRCS), respectively. In 2021, Zhang et al. proposed a new nomenclature for type 5 CRS (secondary CRS): type 5 for acute secondary CRS (ACRCS) and type 6 for chronic secondary CRS (CRCS). [6]

aCRS is thought to be due to the presence of fluid imbalance, neurohormonal activation, arterial underfilling, heightened abdominal pressure, and renal and intensive decongestive therapy. [7,8] ADHF patients most often develop AKI. [9,10] ADHF patients with AKI have high morbidity and mortality rates. The concurrent groups RIFLE (risk, injury, failure, renal function loss, and end-stage kidney disease), AKIN (acute kidney injury network), and Kidney Disease: Improving Global Outcomes (KDIGO) define and stage AKI. [11] These varying AKI diagnostic criteria hinder early diagnosis of CRSs.

AKI is caused by a sudden loss of renal function, resulting in the buildup of waste products and a significant increase in morbidity and mortality rates. It is commonly diagnosed in critically ill patients, with an estimated occurrence of up to 50% in intensive care unit patients. Despite ongoing efforts, the AKI-induced death rate has remained high over the past half-century. Thus, it is critical to investigate novel therapy options for preventing the AKI epidemic. [12] Many studies have found that inflammation and Toll-like receptor-4 (TLR-4) activation play significant roles in the pathogenesis of AKI in ADHF. [12] Noteworthy is that challenges in the search for efficient pharmacological therapy for AKI have arisen due to the multifaceted origin and complexity of the clinical history of patients with CRS. [12]

Despite different diagnostic patterns, individuals hospitalized with ADHF or acute coronary syndrome (ACS) and various comorbidities had 20% to 75% and 3% to 43% rates of aCRS, increasing morbidity and mortality rates. [9,13] AKI was one of the significant risk factors in patients who had cardiac surgery, with a prevalence of 22.3%, potentiating poor outcomes. [10] A recent study found that 25% of patients acquired renal failure (RF) due to cardiac events. [10] Research indicates that 16% of AKI patients get aCRS. [14] An enhanced aCRS mechanistic approach should include assessing initial kidney function, timing, progression, and severity of renal impairment, and incorporating particular biomarkers capable of detecting early kidney injury. Hence, clinical and laboratory characteristics may provide a distinct mix of predisposing, precipitating, and amplifying variables that might impact aCRS development. Therefore, aCRS is a diverse illness that requires a more precise and systematic definition and classification, including factors such as clinical status, renal condition, and therapy. Implementing universally accepted definitions for worsening renal function (WRF) or AKI would be the initial step toward attaining a precise categorization. [8]

In this comprehensive review, aCRS will be discussed thoroughly regarding its epidemiology, pathophysiology, clinical presentation, diagnosis, therapy, and prevention while exploring the unclear points that need further research. To achieve these aims, we searched PubMed, EMBASE, Scopus, Google, and Google Scholar for new articles published between January 2019 and June 2025. Keywords and phrases such as aCRS, CRS type 1 pathophysiology, aCRS therapy, type 1 CRS outcomes, and novel therapy for aCRS were used.

EPIDEMIOLOGY OF ACRS

aCRS is a prevalent type of CRS worldwide, with a rate of 27% to 50% among CRS types. [4] aCRS in admitted patients with AHF varies between 10% and 71% globally. However, a study has observed that the aCRS average prevalence was approximately 32%. [4] It was reported that aCRS affects people of all ages, and it is more often seen in older males, which is linked with unfavorable prognoses. [15] Research conducted in India examined a group of children who were hospitalized with CRS and found that 40.3% of these children had aCRS. [16] The most prevalent subtype of CRS among Indian CRS patients was aCRS (46.1%), [3] which remained at its exact prevalence until 2022. [4] Despite population heterogeneity and AKI definition variations, approximately 25% to 33% of ADHF patients acquire aCRS. [17] However, large-scale population/community-based studies are necessary to determine the exact prevalence of different types of CRS, including aCRS, to predict their prognoses. [15]

ADHF due to ACS leads to acute renal function impairment as a frequent precipitating factor in aCRS. [4] The mortality risk for admitted ADHF patients who develop WRF or AKI is 20% greater than that of those who do not have WRF or AKI. [18] It was reported that CKD, diabetes mellitus (DM), hypertension, and myocarditis are the prevalent risk factors for aCRS among Indian patients. [4,19,20]

PATHOPHYSIOLOGY OF ACRS

The pathogenesis of CRS is a complex process involving several factors and is often identified in advanced stages. [4] ADHF leads to impaired renal perfusion (IRP), sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation, increased central and abdominal venous pressure, increased venous glomerular pressure, oxidative stress species (ROS), and inflammatory responses, which directly and indirectly increase glomerular and interstitial kidney tissue pressure, leading to their damage. These changes lower the glomerular filtration rate (GFR) and cause damage to nephrons, scarring, and fibrosis. While there is a lack of detailed understanding of the mechanisms involved, there is a generally recognized conceptual framework for developing aCRS that includes both hemodynamic and nonhemodynamic linkages. [21] **Figure 1** illustrates the possible pathophysiology of aCRS.

AKI, AHF, aCRS, ischemic heart disease, myocardial infarction (MI), serum creatinine (Scr), central venous pressure (CVP), atrial natriuretic peptide (ANP), and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Hemodynamic mechanism in aCRS pathophysiology

The hemodynamic interactions between the heart and kidneys are triggered mainly by the activation of RAAS and SNS. [4,22] The development of aCRS includes several factors, such

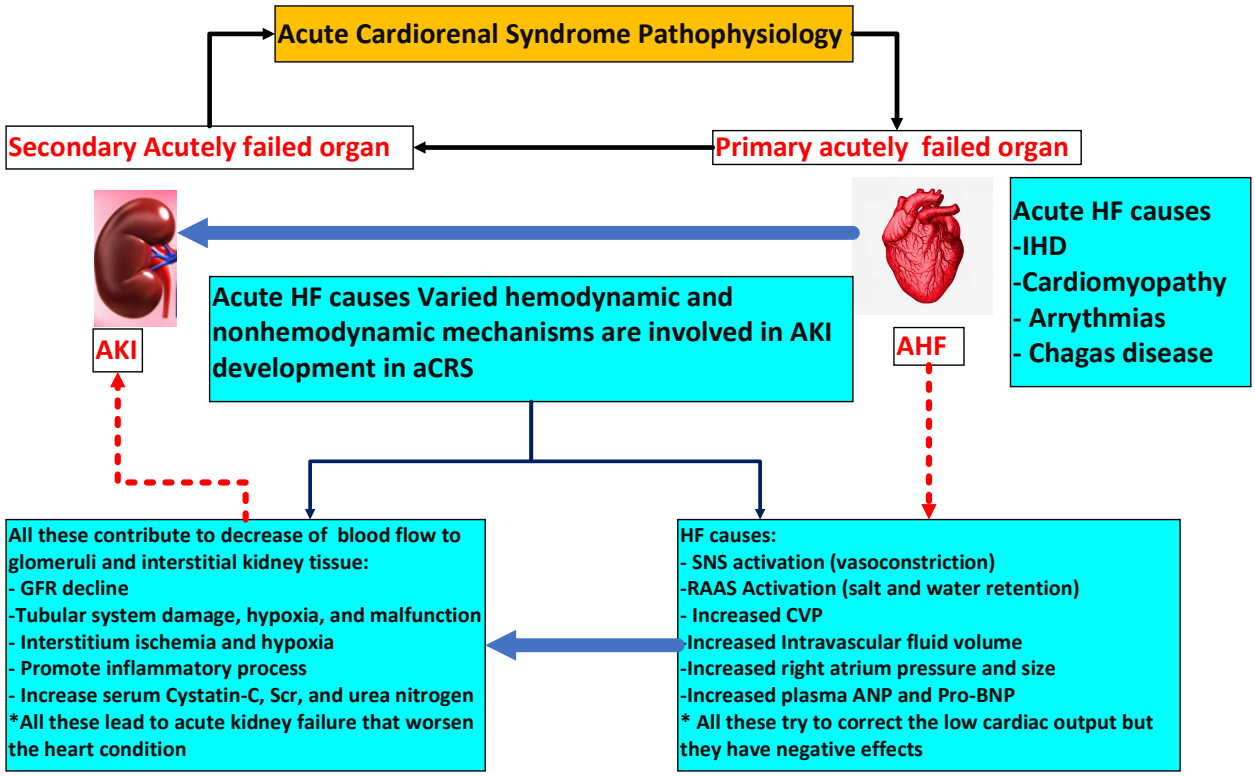

Figure 1: Pathophysiology of acute cardiorenal syndrome.

as hemodynamic signaling, SNS activation, inflammatory and immunological responses, and the disruption of redox homeostasis. [4, 5, 23] Interestingly, activating one component leads to the simultaneous activation of other components, creating a vicious loop. [4, 24]

The decline in cardiac output (CO) and poor systemic arterial circulation filling are the primary initiators of aCRS. [25] Patients with ADHF have an increase in volume overload, resulting in high CVP. Renal dysfunction has a direct correlation with elevated CVP. [26] Elevated CVP increases renal venous pressure (RVP), reduces kidney BF, and leads to inadequate kidney perfusion because of impaired cardiac function. [26, 27] This will lead to a decline in the estimated glomerular filtration rate (eGFR), related to an increased death rate. [28, 29] Diminished renal function contributes to the development of AKI or WRF and ischemic damage to glomerular and nephron tubules, thereby exacerbating aCRS. A decrease in GFR increases Scr levels by ≥25% compared to the first value. The elevation of Scr is usually considered a biomarker of RF.

The RAAS activation is a part of neurohormonal pathways that represent a physiological response to HF and are closely linked to raised mortality and morbidity. [30] It is widely thought that the activation of the RAAS pathway is one of the mechanisms often involved in aCRS. [4] RAAS becomes overactive during the first stages of aCRS. [31] The RAAS is extensively activated in different tissues, including the myocardium and kidneys, which might induce ischemia and deterioration of myocardium and nephron function. [4, 30, 32] Traditionally, the RAAS plays a crucial role in regulating systemic or circulatory functions under physiological limits, which serves unconventionally as a defensive reaction to tissue damage. [33, 34] In ADHF, reduced kidney BF causes RAAS activation throughout the body.

In reduced renal BF, renin is produced, and the SNS is activated. [33] Furthermore, activation of RAAS and SNS causes adrenaline and noradrenaline release, which is mediated via the angiotensin (Ang)-II–mediated pathway, leading to elevated plasma renin levels. [32] Furthermore, Ang-II is a powerful hormone that constricts blood vessels, exacerbating the poor perfusion and damage to the kidneys. Moreover, Ang-II induces oxidative stress and localized inflammatory reactions and stimulates kidney fibroblast transformation into myofibroblasts, which induces local tissue inflammation and fibrosis, triggering a non-conventional RAAS axis development and activation. [4, 35] Additionally, Ang-II prompts the release of aldosterone as part of the RAAS activation. [32] It was advocated that the presence of both high aldosterone and Ang-II induces localized inflammation and fibrosis in cardiac and renal tissue. [4, 35]

In ADHF, RAAS activation occurs as a compensatory mechanism in response to decreased CO and reduced kidney BF. [36] Nevertheless, high plasma renin levels lead to high serum aldosterone levels, which cause increased salt and water retention and heart overload. This results in a drop in the eGFR and exacerbates renal damage in AHF. [37] Persistent RAAS and SNS overactivity are detrimental and result in further cardiac function impairment owing to increased levels of inflammation, oxidative stress, and remodeling of the extracellular matrix (ECM) with fibrosis. [38] The activation of

the aldosterone-induced humoral response triggers further cardiac inflammation, remodeling, and fibrosis, causing HF progression. [32, 37] Additionally, RAAS hyperactivation in the kidney leads to pathological damage by causing the narrowing of renal and extrarenal blood vessels, inflammation, and excess fibrous tissue. [36, 39] Also, aldosterone stimulates the generation of reactive oxygen species (ROS) in tissues, which worsens the inflammatory response and causes damage to both the heart and kidneys. [32]

It was reported that a collaborative function between the natriuretic peptide system (NPS) and RAAS acts as an antagonistic regulator for maintaining the balance of renal and cardiovascular functions. [40, 41] The RAAS and NPS paracrine action is also linked to regulating sodium and water balance in the kidney. [40] Three key natriuretic peptides, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), serve as counter-regulators to the RAAS's actions. [40] ANP and BNP function as diuretic agents, stimulating the development of myocardial fibrosis in HF patients.

Neprilysin is an extensively distributed enzyme attached to cell membranes that breaks down the bloodstream's vasoactive peptides, such as ANP and BNP. This breakdown process leads to a rise in blood pressure during the end-systolic phase. [42] However, in contrast to this action, neprilysin also inactivates the products of the RAAS, including Ang-I, Ang-II, and endothelin 1. [4] Heart failure patients with increased levels of soluble neprilysin and animal models of HF have shown heightened renal neprilysin activity. [43,44] Furthermore, there was a strong association between increased serum levels of soluble neprilysin and negative outcomes. This correlation serves as a reliable indicator of cardiovascular-related deaths in patients with HF and possibly aCRS [44]; however, further studies are required.

Nonhemodynamic mechanism in aCRS pathophysiology

The underlying nonhemodynamic mechanism of aCRS includes ROS, inflammatory mediators, and apoptosis. An imbalance between ROS production and the body's antioxidant defense system's ability to neutralize them leads to damage to different organs, including the heart and kidneys. Under normal physiological circumstances, ROS are generated and controlled in all organs, such as the kidneys and the heart, supporting their cellular functions. [45,46] However, under some pathological or physiological stress situations, the balance of ROS is disrupted, resulting in an upsurge of ROS formation by mitochondria, which leads to tissue damage. [46] The ultimate cause of tissue damage in individuals with aCRS is the dysfunction of mitochondrial metabolism in the cardiomyocytes and renal tubular cells. [46] ROS and RAAS activation in nephron tubular cells causes water and sodium retention, which results in vasoconstriction and promotes SNS activity. [42] The RAAS and SNS overactivity play a significant role in aCRS development. [5]

Cardiomyocytes primarily rely on xanthine, xanthine oxidase, nitric oxide synthase enzymes, and peroxisomes to generate ROS and reactive nitrogen species (RNS). It was reported that AHF patients have experienced a significant rise in the number of ROS indicators. [44] In contrast, the kidney primarily utilizes NADPH oxidase as its primary source of ROS and RNS. [43] However, an imbalance in ROS and RNS levels directly disrupts the functioning of cardiomyocytes and triggers inflammatory reactions. [47] An incremental decline in cardiomyocyte numbers occurs due to heightened ROS, progressing maladaptive cardiac remodeling, and fibrosis. [4,47] Oxidative stress biomarkers, including plasma cystine-C, aminothiols, and glutathione, are associated with an elevated mortality risk. [48] Interestingly, these biomarkers may also have the potential to serve as indicators for patients with aCRS. [4] In addition, the redox-regulatory protein (TRX)-1 is shown to increase the urine fraction in AKI and may be used as a biomarker for ROS in kidney injury. [49] ROS is a significant factor in the development of AKI and is one of the main contributing factors. [50] Nevertheless, the specific effects of oxidative stress on the pathophysiology of CRS remain unclear, and the absence of appropriate biomarkers for patients with CRS poses challenges for identifying oxidative stress-induced damage to the heart or kidneys. New research projects are required to evaluate these issues further.

Moreover, myocardial ischemia, which causes swelling and damage to the myocardium, is a leading factor in the development of AHF, leading to various comorbidities in aCRS. After ischemic damage, decreased blood flow caused by cardiac dysfunction leads to RAAS and SNS overactivity and redox systems in the heart. This, in turn, triggers pathological inflammation in patients with AHF. [51] After ischemic damage in a rat model of MI, there is a noticeable increase in macrophages migrating into the kidneys, activating monocytes with CC chemokine receptor 2(+) ED-1(+) and macrophages, and an increment of nuclear p65 in the kidney of induced MI rats, indicating an inflammatory response in the heart, inducing kidney injury. [52] Ang-II is increased chiefly in the RAAS activation and plays a significant role in RAAS-induced inflammatory responses in the NF-κB and Activator protein 1 (AP-1) pathways. [53] Generally, in aCRS, there is a significant increase in the RAAS axis activity and inflammation. [4,53] Ang-II stimulation is linked to the increased production of inflammatory cytokines (such as alpha-tumor necrosis factor (TNF-α), interleukin-6 (IL-6)-6, and interleukin-1β by cardiomyocytes. Similarly, it has been proposed that the TNF-κB pathway plays a role in mediating the inflammatory response in the kidney. [52] Furthermore, high C-reactive protein (CRP) levels are associated with significant mortality in patients with ADHFs. Studies investigated the relationship between inflammatory markers and aCRS and reported that inflammatory mediators are linked directly to aCRS development, which may provide valuable prognostic information. [7,53] The association between the raised inflammatory biomarkers and aCRS is highly evident, as reported by different studies. [53,54]

Years ago, a novel notion emerged regarding the detrimental effects of inflammatory responses caused by AKI or AHF on the cardiac and renal tissues. These reactions destroy tissue via remodeling and apoptosis, exacerbating initial damage. Animal models showed the death of nephron tubule cells, which might potentially cause further harm to the kidney. [55] In addition, kidney cell apoptosis is linked to increased levels of TNF-α and IL-6, [52] indicating the involvement of inflammation-induced pathological apoptosis in AKI-related damage.

ACRS MOLECULAR PATHOPHYSIOLOGY

Recently, new proteomic biomarkers and miRNAs linked to CRS have enabled the identification of novel molecular pathways. C-X-C chemokine receptor type 4 (CXCR-4), also called (fusin or cluster of differentiation 184 (CD184)), is a human protein encoded by the CXCR4 gene. In the context of acute cardiorenal interaction, there is an overactivation of inflammatory responses aimed at reducing the initial damage to the heart, but this worsens the harm to both the heart and the kidney. CXCR4 is a chemokine receptor connected with G proteins and is involved in the movement of immune cells towards damaged tissues. [56,57] CXCR4 serves as the specific receptor for SDF-1 and contributes to the exacerbation of inflammation-induced cardiorenal fibrosis. [56] It has been reported that in acute ST-segment-elevated MI. [58] The signaling of CXCR4 following cardiac damage may be used to predict negative outcomes. Renal cell types with long-lasting CXCR4 expression are similarly linked to the injury-induced fibrotic response. [58,59] Hypertension is frequently observed as the underlying cause of aCRS. It is linked to the overactivation of the neurohormonal RAAS system, inflammatory reactions, and the development of CRS. [56]

A substantial association exists between acute inflammation and cardiorenal fibrosis. The activation of stromal-derived factor (SDF)-1 by angiotensin II is linked to the infiltration of immune cells that promote fibrosis at the site of local inflammation. [56,59] In addition, the stimulation of cardiomyocytes by neurohormonal or Ang-II leads to an excessive production of SDF-1. [60] SDF-1 levels that are higher than normal interact with CXCR4 and encourage the infiltration of fibroblasts during cardiorenal fibrosis. [56,60] The acute inflammatory response in the myocardium leads to the secretion of inflammatory cytokines and chemokines, including TNF-α, IL-6, IL-18, and MCP-1, by the immune cells that have infiltrated the damaged vicinity of the heart or the kidney. [61,62] aCRS patient samples show increased levels of proinflammatory cytokines in circulation. [61] The upregulation of TNF-α, MCP-1, VCAM-1, and ICAM-1 in the renal tissue in aCRS aims to induce an inflammatory reaction in the kidney. [62] These findings indicate that both local and systemic inflammatory reactions play a crucial role in the communication between organs, which is a key factor in developing all CRSs, especially the aCRS. [62] A recent study has documented the collaboration between inflammation, the RAAS, and the angiotensin type-1 (AT-1) receptor-mediated NF-κB pathway signaling. [63] Although the specific mechanism has not yet been examined, proinflammatory chemicals have been identified as prospective biomarkers owing to the connection between inflammation and aCRS Pathogenesis.

PRESENTATION AND DIAGNOSIS OF ACRS

aCRS is characterized by AHF, which can present with signs of overloading such as edema, tachypnea, and orthopnea. Furthermore, due to AKI, there may be a reduction in urine production or oliguria. Vomiting and nausea due to uremia are common features. Pulmonary edema occurs in severe cases. Chest radiography, electrocardiography, and echocardiography should be performed. Additionally, the usual kidney function panel for Scr, BUN, electrolytes, and ultrasound of the kidneys is a mandatory investigation in aCRS cases. Other biomarkers of aCRS are discussed in the following sections.

ACUTE CARDIORENAL BIOMARKERS AND THEIR CHALLENGES

Measurements of eGFR, BUN, and Scr levels were used as initial diagnostic tools to identify AKI in aCRS. In individuals with CRS, the eGFR is calculated based on creatinine levels in the blood. Scr levels are not an early AKI indicator of acute ACR. [64] The evaluation of early AKI is insufficient when using eGFR assessment. [64] Although there is a lack of conclusive evidence, individuals with ADHF who developed AKI early on had elevated blood and urinary neutrophil gelatinase-associated lipocalin (NGAL). Lastly, CRS encompasses nonhemodynamic mechanisms such as inappropriate SNS and RAAS activation and inequity between nitric oxide and ROS that aggravate the immunological signaling and inflammatory mechanisms. [4] The available and novel biomarkers are discussed in the following paragraphs.

Cystatin C (CysC) belongs to a cysteine protease inhibitor. It has a molecular weight of 13.3 kilodaltons and is produced by all the nucleated cells. CysC is readily filtered into the urine, making it valuable for evaluating renal function and GFR calculation. In contrast to serum BUN and Cr, CysC does not undergo further reabsorption or secretion by parts of the nephron. [65] Compared to Scr and BUN, serum (S) CysC is a more precise endogenous surrogate indicator for GFR. Measuring serum (S)CysC in ACS has enhanced the early risk assessment upon admission, indicating its potential as a biomarker for aCRS. [66] All these characteristics have made CysC a superior indicator of functional assessment in AKI compared to other AKI biomarkers (Scr, BUN, and GFR).

SCysC levels may be influenced by several variables, such as excessive body fat mass, diabetes, overweight, inflammation, obesity, and others, including thyroid, [67–69] but are not significantly affected by age or muscle mass, like BUN or Scr. [70] Furthermore, a study found that individuals with aCRS showed only a slight variation in their SCysC levels. [71] In addition, SCysC levels increase in AHF patients who have no kidney dysfunction, rendering it an inaccurate marker for detecting individuals with aCRS. [72] In addition, male gender, elevated C-reactive protein, and smoking independently influence the SCysC level, regardless of the presence or absence of AKI. [72] While there is a strong correlation between SCysC, eGFR, and renal impairment in various ages, there is currently a lack of real-world assessment in samples of patients with aCRS. [73] Hence, more extensive investigatory data are required.

BUN is often used with Scr to identify AKI. [74] Urea is easily passed through the glomerulus and reabsorbed by the nephron's tubular system, which secretes it in different parts. [75] Elevated BUN values are indicative of deteriorating renal function. [75] Hyperactivation of the RAAS, SNS, and the neurohormonal system in aCRS leads to increased BUN levels, indicating kidney function. [76] An increased BUN/Scr ratio may be used as an indicator of GFR decline in aCRS and poor prognosis.

The wide range of BUN values limits its effectiveness in identifying aCRS. BUN levels are affected by several variables

unrelated to kidney function, including dietary protein consumption, increased protein breakdown, high-dose steroids, bleeding in the gut, and hepatic urea production. [77] There is a clear correlation between elevated BUN levels and adverse outcomes in individuals with aCRS. [78]

Elevated Scr levels are often used to diagnose aCRS compared to other CRS types. [79] Despite some lack of specificity, it is now considered a reliable method for predicting and diagnosing kidney damage. [80] Increased Scr levels from baseline may predict AKI development in patients following cardiac surgery up to the day following surgery. Moreover, a high Scr level is linked to more extended hospital stays and a much higher risk of complications. [80–82] The normal Scr range is 0.6 to 1.2 mg/dL (61.9–114.9 µmol/L) in men and 0.5 to 1.1 mg/dL (53–97.2 µmol/L) in females. The deterioration of AKI in patients admitted for ADHF is strongly associated with elevated Scr levels. In a study, 36% of the included patients had Scr levels >2.0 mg/dL and had worsened AKI after admission. [83] Recently, it was reported that SCr is utilized to diagnose AKI, although SCr level has a limited value in distinguishing between acute damage and volume depletion. On the other hand, neutrophil gelatinase-associated lipocalin (uNGAL) distinguishes between the two conditions. Hence, uNGAL is used in the emergency medical services department. [84] Although Scr is an essential biomarker for WRF, it cannot reliably measure the severity of RF during acute injury-induced alterations. [85] The Scr level is not affected by minor to moderate changes in the GFR and only rises after a significant decrease in GFR. [86] In addition, creatinine is synthesized in the liver, and the Scr levels may be affected by factors such as liver illness, fever, or age, which might hinder the accuracy of diagnosis. [85] Although Scr was used as a diagnostic measure for AKI in the Indian study, due to many constraints, Scr is not very dependable in identifying early AKI in CRS patients. [78]

GFR quantifies the volume of the filtrated plasma and is used as a significant surrogate marker of kidney insufficiency. If GFR declines below the normal baseline, it suggests nephron dysfunction. [4] Normal (>90 mL/min/1.73 m^2) or moderate renal insufficiency (>60–<90 mL/min/1.73 m^2) is indicated by GFR. [87] Venous congestion in patients with CRS leads to inadequate kidney perfusion. Kidney hypoperfusion leads to a decline in the GFR and is a significant risk factor for WRF and AKI. The regulation of GFR is controlled by RAAS and SNS, which are the imbalance between nitric oxide and ROS via the renal vessel's diameter change in CRS, producing renal and coronary BF reduction in HF. [4,5,88] Assessing eGFR at admission provides a moderate indication of the likelihood of AKI in HF patients. Elevated death risk in hospitalized patients accompanies the decrease in GFR in CRS. [89] Research conducted in India found that lower eGFR was related to worse outcomes in hospitalized and discharged patients with CRS. [78]

GFR in AKI is measured by assessing Scr and urine Cr; however, these markers do not consistently align with the real GFR. [90] The incorrect GFR calculation delays the early detection of AKI. Furthermore, the lack of precision in calculating eGFR leads to inaccurate predictions about the deterioration of AKI. [91] Hence, it is necessary to identify novel and precise biomarkers.

Novel biomarkers for aCRS

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2 or siderocalin, is a small glycosylated protein. [4] And it is secreted by neutrophils under stress conditions, indicating nephron tubule and cardiomyocyte acute damage. [92,93] Moreover, NGAL is upregulated in kidney tubular cells as an early response to ischemic kidney damage or renal toxicity. [4,5,92,94] Patients who underwent heart surgery and ACS showed a significant increase in blood and urine NGAL levels, with a tenfold or greater increase. These elevated levels serve as early indicators of AKI onset. [95] The study conducted by Macdonald et al. found a correlation between hospitalized ADHF patients and elevated NGAL levels compared to their baseline levels. [96] This increase in NGAL levels was associated with increased AKI risk and death rate. Unlike Scr, elevated NGAL may be observed within 1-3 hours after cardiac insult in these individuals. This finding is further corroborated by evidence from animal models. [92,93]

The RIFLE criteria determine the diagnosis of AKI or WRF in 25% to 40% of patients hospitalized with ADHF. [95] Measuring NGAL levels upon admission may help diagnose WRF early in aCRS. NGAL levels over 130-170 ng/mL are associated with worse clinical outcomes. [95] The levels of urine NGAL increased by 100 times, while the levels of plasma NGAL increased by a factor of 20. This increase in NGAL levels has enabled the early prediction of AKI and AHF, even before a substantial change in Scr was reported. [97]

Although serum and urine NGAL levels are generally recognized as early biomarkers of AKI in CRS, their usefulness is limited owing to variations in threshold levels and individual responses. Nevertheless, using high-sensitivity assays to assess plasma NGAL levels may enhance the accuracy of diagnosing AKI in aCRS. [98] It is becoming well-documented that measuring plasma levels of NT-proBNP, Cystatin C, and NGAL, as long as their baseline values are known, might significantly enhance the diagnostic accuracy of CRS in ADHF or AHF cases. [94,99]

Cardiomyocytes generate BNP as a preventative measure against volume overload or pressure increase. [100,101] BNP reduces ventricular stress by increasing GFR and decreasing vascular resistance in the kidney tubule vessels. [4,101,102] In stress conditions, BNP, NT-proBNP, and proNP convertase cleave pro-BNP, increasing pro-BNP synthesis. [100] Conversely, the hyperactivation of RAAS and SNS impedes the activity of BNP and exacerbates the fluid overload. [101] In AHF and post-MI, a transient elevation in NT-proBNP and pro-BNP concentrations occurs. [94,103] Pro-BNP plasma levels are higher in CRS patients who did not survive the hospital stay than those who did. [89] A high NT-proBNP level at baseline can significantly predict aCRS. [103] Survival and rehospitalization are both enhanced by a decrease in serum NT-proBNP. [104] Unfortunately, elevated NT-proBNP levels are indicative of age-related health complications. NT-proBNP levels may be substantially elevated from baseline in elderly individuals without cardiovascular complications. [105] This constrains the utility of NT-proBNP as a distinct protein biomarker for aCRS in older adults. A multitude of fascinating biomarkers have been discovered in various types of CRS; however, their exploration remains limited. For example, the thickness of the LV wall increases, and the serum

hepcidin level increases even without HF. [106] Hence, its significance as a biomarker for aCRS development is limited.

Clinical investigations of acute and chronic CRS use a limited number of protein biomarkers. Recent studies have investigated biomarkers for CRS, such as KIM-1, N-acetyl-κ-d-glycosaminidase (NAG), ST2, Galectin-3, liver-type fatty acid-binding protein (L-FABP), insulin-like growth factor–binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinase 2 (TIMP2).

When cells exocytose or disintegrate, healthy tissues release a lysosomal enzyme, N-acetyl-β-d-glucosaminidase (NAG). Due to its high molecular weight, the glomerulus is unable to filter it, resulting in minimal quantities of it in the urine. [4,107] Nevertheless, damage or lesions in the nephrons lead to a rapid increase in urine NAG levels, indicating AKI. Patients with AKI and hypertension have increased levels of NAG, [108] This may contribute to the development of aCRS. Other markers in the urine are insulin-like growth factor (IGF)-binding protein-7 (IGFBP) and tissue inhibitors of metalloproteinases-2 (TIMPs-2), which are biomarkers that indicate cell cycle arrest. The levels of urine IGFBP7 and TIMP2 are increased in early AKI patients, which aligns with the findings of NGAL. [109]

KIM-1, a transmembrane receptor, is a type-1 glycoprotein found on the surfaces of epithelial cells. [110] The proximal tubular epithelial cells can also lead to AKI. [110] Following injury, renal tubular epithelial cells exhibit the expression of KIM-1 in the urinary compartment, leading to the identification of KIM-1 in the urine of AKI patients. [111] A study found a correlation between the elevated level of KIM-1 in patients with chronic CRS and NGAL. [112] The rapid and significant increase in urine KIM-1 in AKI makes it a promising biomarker for diagnosing aCRS. [113] A recent study conducted at many centers found that KIM-1 is a reliable indicator of AKI in ADHF patients. [83] Sabbisetti et al. found that cardiac surgery patients who had AKI had higher levels of plasma KIM-1 compared to those who did not develop AKI. [114] In contrast, another study reported that urinary KIM-1 levels did not significantly predict aCRS. [115]

GalACTIN-3 (Gal-3) is a lectin that binds to β-galactoside and has a molecular weight of 30 kDa. It plays a role in cell interactions and between cells and the ECM. Gal-3 is released into the bloodstream and urine by cells that are injured or experiencing inflammation. [116] It has been shown that this is a reliable early marker of AHF. [116] Reduced GFR has a more significant impact on Gal-3 levels in HF patients than in individuals without heart failure. [117]

In addition, cardiac troponin T (cTnT) and cTnI are sensitive biomarkers that can be used to predict and diagnose AHF and ADHF. Therefore, they may also serve as biomarkers for aCRS. It is vital to investigate aCRS since increased levels of cardiac troponins are associated with reduced GFR and higher mortality rates in CKD patients. [5,118] Patients with AHF who had increased levels of TNFα had higher mortality rates. [119] Assessing the levels of TNF-α and other inflammatory biomarkers, such as IL, may be appropriate for individuals with aCRS. Cardiac involvement in aCRS is often identified using echocardiographic measurements in Indian clinical studies. [19,78] India has a limited number of CRS biomarkers, which hinders the early detection of AKI in future CRS patients.

Finally, microRNA (miRNAs) are internally preserved RNA molecules that are involved in regulating gene expression after transcription. [120] The miRNA molecules are more resistant to degradation. [121] miRNAs like miR-21, miR-320, and miR-208 are related to aCRS with variable degrees. [120] Notably, miRNA-21 is increased in both the heart and kidney during acute illnesses, which contributes to fibrosis development. [122,123] miRNA-21 is found in the urine of AHF and AKI patients. [4,124] The miRNA-21 pro-fibrotic properties in CRS have been investigated as a possible focus for diagnosis and treatment. [120,122] miRNA-21, miRNA-200b, and miRNA-93 have been detected in individuals with hypertension, and they might help diagnose aCRS. [125] However, this may reduce the ability to diagnose aCRS in hypertensive patients.

Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), soluble VEGF receptor-1 (sFlt-1), PDGF/sFlt-1 ratio, Soluble Suppressor of Tumorigenicity-2 (sST2), Myeloperoxidase (MPO), Procalcitonin, Copeptin, mid-regional proadrenomedullin (MR-proADM), liver-type fatty acid-binding protein (L-FABP), and urinary cofilin-1 are other cardiac biomarkers. Interleukin-18 (IL-18), tubular biomarkers such as alpha-1 microglobulin (A1M), liver-type fatty acid-binding protein (L-FABP), Urinary angiotensinogen (uAGT), urinary vascular endothelial growth factor, tissue Inhibitor of metalloproteinase-2 (TIMP-2), and proenkephalin (PENK) are also new renal biomarkers. There is no evidence that new biomarkers can diagnose and determine the prognosis of aCRS, although they may be utilized in conjunction with established biomarkers. They may improve the diagnosis accuracy, treatment, and prognosis of such patients, together with established biomarkers. However, further detailed research is required.

CRS is the primary determinant of baseline risk factors, including coronary artery disease, DM, hypertension, and atrial fibrillation, owing to an active lifestyle. [126] Such risk factors exacerbate aCRS pathogenesis in patients with acute HF or CKD. aCRS is challenging to diagnose owing to the absence of prognostic characteristics despite the use of biomarkers for cardiac or renal damage. Scr, BUN, BNP/NT-pro BNP, and cardiac troponin I and T have significant limitations in predicting the development of aCRS. [108] In the past few years, there has been an expansion in the body of research on AKI, AHF, and aCRS biomarkers, facilitating straightforward and exceptionally predictive biomarker inquiries. Biomarkers such as hepcidin, soluble urokinase plasminogen activator Receptor, Placental growth factor, urine protein/Cr ratio, and urinary cofilin-1 are novel in aCRS. [4,104,106,127,128] Existing biomarkers with inadequate predictive value necessitate the development of new aCRS-specific biomarkers to improve molecular pathophysiology and prognosis. Due to the extensive pathophysiological profile of aCRS, further research is required to identify CRS-specific biomarkers to determine the sensitivity and specificity of the available and novel biomarkers.

OUTCOME OF ACRS

aCRS is associated with more negative outcomes. [129] ACRS has higher death rates among hospitalized patients with ADHF and AKI. [130] Therefore, it is crucial to establish an accurate early diagnosis to minimize the mortality rate. Furthermore,

clinical studies indicate that hospitalized aCRS patients have a higher death rate than patients with cardiovascular dysfunctions such as AHF or ADHF. This suggests that the time the condition progresses is a risk factor. [131] The AKI onset time is another crucial determinant in individuals with aCRS. Early start of AKI is linked to a greater likelihood of hospitalization, whereas the percentage of admitted patients with late-onset AKI is much lower. [132] A recent study found that the death rate for patients who had AKI during the first 5 days of admission was 13.8%, and those who developed AKI later were 11.8%. [129]

ACRS THERAPY

Considering the constraints of reduced kidney function in correcting excessive fluid volume and the frequent connection between kidney dysfunction and death in patients with HF, the successful management of aCRS might enhance patient outcomes. Unfavorable prognosis in HF is associated with the development of AKI, leading to diminished GFR, which is indicative of a more advanced stage of heart disease. In this scenario, improving renal function alone may not lead to improved patient outcomes. Hence, measures to simultaneously improve acute HF and AKI should be the goal of achieving a good prognosis. Fluid resuscitation in hypovolemic patients and fluid removal in overloaded patients by diuretics and possibly ultrafiltration will improve cardiac pumping function. These interventions are leading measures for improving CRS and outcomes.

Diuretics

Loop diuretics are the primary fluid removal treatment in aCRS. [133] No clinical experiments have compared furosemide, bumetanide, torsemide, or ethacrynic acid. Hence, there was no obvious winner. Dose Optimization Strategies Evaluation (DOSE) examined the dosage scheme in 308 patients (1:1:1:1) to low-dose (equal to oral dosage) or high-dose (2.5 times oral dose) intermittent parental dosing or continuous drip therapy. Intermittent and drip techniques did not affect dyspnea, fluid changes, Scr levels, hospital stay length, rehospitalization, or mortality rates. The high-dose arm subjects showed less dyspnea, more significant volume reduction, and more AKIs than the low-dose arm. [134]

Adding a second-site diuretic to loop diuretics may increase the urine flow in clinical practice. Unfortunately, there is insufficient evidence to support this widespread therapeutic practice. Therefore, second-site diuretics (chlorothiazide or metolazone) were tested with uncertain results. Often, the cost or ineffectiveness of metolazone oral absorption determines the decision. A retrospective study by Moranville et al. compared chlorothiazide to metolazone in ADHF-renal impairment patients of GFR 15 to 50 mL/min, revealed that the chlorothiazide group had a more extended hospital stay, metolazone increased urine production non-significantly, and side events were similar. [135] Although encouraging, the retrospective analysis made it impossible to identify whether the changes were attributable to treatment methods or patient sickness. However, the second-site diuretic method might produce metabolic derangements such as hypokalemia, hyponatremia, hypomagnesemia, and metabolic alkalosis. [136]

Inotropes

In aCRS with markedly reduced CO, inotropic drugs such as dobutamine or milrinone may improve renal perfusion by enhancing heart function. [133] However, no objective evidence exists regarding the efficacy of this strategy. Milrinone did not enhance renal function in the OPTIME-HF trial. [137] The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial compared dobutamine to levosimendan (a cardiac calcium sensitizer that increases contractility) and found no differences in RF rates. [138] Inotropes may treat aCRS if CO is significantly impaired; however, they can cause fatal arrhythmias.

Dopamine

ADHF has extensively researched low-dose dopamine stimulation of dopamine (D)1 and D2 receptors to improve renal blood flow, glomerular filtration, and urine output. A small experiment found that low-dose dopamine protected 20 individuals' kidneys. [139] However, extensive studies have not consistently reported similar benefits. The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) study compared low-dose furosemide with 5 µg/kg/min dopamine against high-dose furosemide alone in 60 patients. There were no changes in total diuresis, hospital stay, 60-day mortality, or rehospitalization rates, although dopamine treatment reduced 24-hour renal dysfunction (6.7% vs 30%). [140] The Dopamine in Acute Decompensated Heart Failure II trial compared 161 ADHF patients to high-dose furosemide, low-dose dopamine (5 µg/kg/min), or low-dose furosemide. This study evaluated dyspnea, renal function, length of stay, 2—and 12-month all-cause mortality, and HF hospitalization. None of the results improved with dopamine. [141] Finally, in the Renal Optimization Strategies Evaluation (ROSE) trial, 360 patients with ADHF were assigned to receive nesiritide or dopamine against a placebo. Urinary output, cystatin C levels, and clinical improvements were not different between dopamine (111 patients) and placebo (115 patients); nevertheless, dopamine increased tachycardia risk. [142] There is no evidence of regular dopamine use in aCRS.

Nesiritide

The natriuretic effects of recombinant brain natriuretic peptide (nesiritide) increase the urine output. The BNP-CARDS experiment was the first to test this hypothesis. BNP-CARDS found that a 48-hour infusion of nesiritide (39 patients) or placebo (36 patients) in ADHF patients who had renal impairment (EGFR, 15–60 mL/min) could not lower the Scr increase by 20%. [143] The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) assessed nearly 7000patients with ADHF using a similar technique. For 24 h and up to 7 days, 3496 and 3511 patients received nesiritide and placebo, respectively. Nesiritide did not improve dyspnea at 6 and 24 hours, creatinine alteration, or the composite endpoint of rehospitalization or death at 30 days. [144] The ROSE study compared nesiritide (117 patients) to placebo (115 patients) for urine production volume, renal function (cystatin C change), and decongestion (urine sodium, weight loss, and NT-proBNP change) at 72 hours. Nesiritide did not affect any parameter. [142] In ADHF patients with pre-existing renal impairment (eGFR 2– 60 mL/min), a single-center Mayo

Clinic trial compared nesiritide (37patients with a placebo (35 patients). This researcher discovered that nesiritide reduced Scr and BUN levels but did not affect diuretic responsiveness, hospitalization length, or rehospitalization rates. Nesiritide decreased serum endothelin but not ANP, renin, NT-pro BNP, angiotensin II, or aldosterone. [145] Overall, nesiritide does not seem to protect against ADHF-induced AKI.

Antidiuretic hormone antagonists

ADHF has been used to investigate the vasopressin antagonists for diuresis and hyponatremia. The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) trial was the first to examine vasopressin antagonists. In the ACTIV study, Tolvaptan enhanced urine output and lowered body weight, which utilized three dosages (77 mg, 78 mg, and 84 mg). A post-hoc ACTIV trial analysis of renal impairment (BUN > 29 mg/dL) in patients with severe overload showed a 60-day survival advantage. [146] In a similar 2-trial design, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVERST) study compared 2061 (placebo patients) to 2072 patients who received 30 mg/day of Tolvaptan within 2 days of admission. The tolvaptan group had weight loss and increased dyspnea immediately; however, it did not affect all-cause mortality. [147] or cardiovascular or HF hospitalization rates for 24 months. [148] These findings imply that vasopressin antagonists may increase diuresis abruptly but not in the long term.

Adenosine A1 receptor antagonists

Adenosine receptor antagonists used to prevent renal vasoconstriction in patients with ADHF have also been studied. First, a trial investigated the effects of rolofylline (an adenosine A-1 antagonist) in patients with ADHF with a GFR of 20 to 80 mL/min. In this study, 27 patients received a placebo, 29 received 2.5 mg, 31 received 15 mg, 30 received 30 mg, and 29 received 60 mg/24 h of rolofylline for 72 h. On day 1, rolofylline enhanced urine production; on day 2, it improved renal function. [149] The Placebo-Controlled Randomized Study of the Selective A1-Adenosine Receptor Antagonist (Rolofylline) for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess the Treatment Effect on Congestion and Renal Function (PROTECT) study investigated the efficacy of rolofylline in treating patients with ADHF and volume overload. This study specifically focused on assessing the effects of treatment on congestion and renal function. The study investigated rolofylline effects in 1356 compared to placebo (677) patients with ADHF who had a GFR of 20 to 80 mL/min. Rolofylline resulted in more significant weight loss compared to the placebo over the 14 days, despite no alteration in renal function. [150] In a subgroup study of severe baseline renal impairment (GFR < 30 mL/min), rolofylline lowered the 60-day endpoint of cardiovascular or renal mortality and hospitalization. [150]

The REACH-UP trial, which investigated the impact of rolofylline (36 patients) versus placebo (40 patients) in patients with ADHF and GFR 20 to 60 mL/min, concluded with an analysis of the effects of injectable emulsion (KW-3902) on the signs and symptoms, renal function, diuresis, and clinical outcomes in patients hospitalized with renal function and HF deterioration requiring intravenous therapy. Although it did not significantly impact renal function, roofline reduced the 60-day combined endpoints of renal or cardiovascular hospitalization or mortality to a moderate degree. [151] In summary, rolofylline treatment did not enhance outcomes related to aCRS.

Steroids

Corticosteroids may enhance fluid and salt retention, so their use in ADHF might be contentious. Corticosteroids enhanced the response to diuretics and kidney function in 13 ADHF patients who failed sequential nephron blockade. [152] In 35 ADHF patients, prednisone therapy increased urine volume, lowered uric acid, decreased dyspnea, and improved renal function. [153] The Coronary Outcome Prevention Effectiveness of Glucocorticoids in Acute Decompensated Heart Failure (COPE-ADHF) trial followed these encouraging outcomes. This single-center trial assigned ADHF patients to a placebo or to receive corticosteroids, and they measured urine volume, Scr, and cardiovascular mortality after 30 days. [153] Another study also reported that corticosteroids enhanced renal function, urine production, and mortality (3/51 vs. 10/51 placebo). [154] Hypothesized pathways for corticosteroid benefits include stimulation of natriuretic peptides effects or renal vasculature dilation via nitric oxide route or dopaminergic system activation. [136]

Serelaxin

During pregnancy, recombinantly produced human relaxin-2 (a peptide hormone prevalent) aids cardiovascular and renal adaptations and may benefit aCRS. [155,156] On day 2, serelaxin lowered SCr, BUN, and CysC fluctuations in the Relaxin in Acute Heart Failure (RELAX-AHF) study. This investigation found that CysC alterations worsened renal function and increased 180-day mortality. [157] The serelaxin mechanisms by which it reduces or prevents renal impairment are unclear, as it did not enhance diuretic efficiency as was suggested. [158]

Ultrafiltration

Ultrafiltration involves the removal of fluid using an extracorporeal circuit. It is usually indicated in severely overloaded patients with ADHF and impaired renal function and is resistant to diuretics.

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial showed the benefits of ultrafiltration in ADHF. This study randomized 200 patients with ADHF to receive ultrafiltration or loop diuretics. Ultrafiltration enhanced volume removal without affecting renal function and decreased 90-day rehospitalization. [159]

Ultrafiltration did not outperform medical therapy in patients with aCRS in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure study (CARESS-HF). Under ultrafiltration, 188 CARESS-HF patients had higher renal dysfunction risk, no volume removal differences, and no significant change in 90-day rehospitalization rates. [160] CARESS-HF's medical treatment arm was more uniform and aggressive, but UNLOAD's ultrafiltration arm was earlier, which may have clarified these disparities. CARESS-HF patients with ultrafiltration had higher renin activity and no aldosterone level difference, despite the hypothesis that

ultrafiltration would reduce RAAS activation due to fluid volume reduction. [161]

Two meta-analyses and one review reported that ultrafiltration was more successful at volume reduction than medical treatment in ADHF but did not impact rehospitalization or death rates. [136,162,163] Although the ultrafiltration in aCRS, the vascular access installation, and bleeding concerns are addressed, ultrafiltration in aCRS is not routinely used. [133]

Continuous renal replacement therapy (CRRT) in aCRS

aCRS may require CRRT for volume elimination and solute clearance, as renal function declines. Unfortunately, clinicians have limited data on patients with advanced aCRS. An Egyptian trial that investigated 40 patients who responded to intravenous furosemide or CRRT revealed that CRRT patients lost more weight and spent less time in the ICU. However, dialysis reliance and 30-day mortality did not change. [164] Results from two single-center investigations with advanced aCRS necessitating CRRT. Ultrafiltration was conducted for 63 aCRS patients at the Cleveland Clinic; 37 aCRS patients switched to CRRT owing to decreasing renal function; out of these patients, 20 patients died. [165] Another retrospective research assessed rescue CRRT in 37 advanced aCRS patients; 25 hospitalized patients died. [166] The Cleveland Clinic and the University of Alabama-Birmingham found that patients with advanced aCRS who needed CRRT had a 60.8% in-hospital death or palliative home discharge rate. Further research is required to avoid these poor outcomes.

Other therapies under investigation

However, none of the existing aCRS therapies enhance outcomes, although numerous clinical studies have explored new approaches in Belgium. There is an ongoing study on spironolactone and acetazolamide to strengthen natriuresis in congestive HF (Diuresis-CHF trial), but the results have not yet been officially published. Another study compared the combined effects of furosemide and hypertonic saline compared to furosemide alone in ADHF and kidney impairment (GFR<60 mL/min). Renal function, hospital stay, diuretic response, weight reduction, readmission rates, BNP levels, and cost analyses were the outcomes. However, the findings of this study were unavailable.

A Swedish trial (Dobutamine for Renal Function in Heart Failure (ELDOR) examined the effects of levosimendan and dobutamine on renal perfusion. Renal BF, renal vascular resistance, GFR, renal oxygen extraction, central hemodynamics, consumption, and filtration fraction were studied. However, the final report has not yet been released.

A therapy for aCRS has not addressed inflammation despite its importance in its pathogenesis. According to preclinical investigations, IL-6 mutant mice exhibited resistance to renal injury and mortality induced by HgCl2. [167] And IL-6 has adverse inotropic effects in isolated cardiomyocytes, [168] and IL-6 causes skeletal muscle atrophy in rats. [169] Inhibition of the IL-6 pathway may help resist inflammation. Therefore, IL-6 antagonism may enhance cardiac and kidney functions, making it suitable for aCRS patient therapy. Tocilizumab (a humanized IL-6 receptor antibody) may enable further studies on this concept. Anti-inflammatory effects may have an impact on corticosteroid benefits. However, the cardiac outcome prevention by glucocorticoids in the Acute Decompensated Heart Failure (COPE-ADHF) study did not assess their effectiveness. Corticosteroids would require additional research for the treatment of patients cheaply. Finally, cytokine profiling may enrich the aCRS patient pool for future anti-inflammatory drug clinical trials.

Further work is necessary to establish whether the treatment option for aCRS should be based on the severity of AKI. An escalating severity of AKI leads to a higher possibility of negative outcomes. However, it is still unclear whether various therapies provide advantages for individuals with varying degrees of renal impairment. Future research endeavors focusing on delineating the results of distinct treatment approaches categorized by the degree of renal function impairment may shed light on the specific patient populations that benefit from many alternative therapies for aCRS.

Renin-angiotensin system antagonists, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNI), and angiotensin II receptor blockers (ARB), as well as the role of sodium-glucose co-transporter 2 inhibitors, are newly invented therapies for aCRS. ARNIs may provide a beneficial treatment alternative for certain patients with aCRS, particularly in individuals with heart failure and mild to moderate renal impairment. However, their use necessitates careful consideration of individual patient characteristics, potential risks such as hyperkalemia, and a thorough evaluation of the benefits versus risks.

Currently, there is no consensus on the definition of AKI in aCRS. As previously mentioned, the use of the RIFLE, AKIN, and KDIGO guidelines and definitions of AKI and diuretic responses is beneficial in distinguishing outcomes in patients with aCRS. Nevertheless, establishing a consensus on a precise AKI definition in aCRS will significantly enhance the progress of the discipline, enabling the systematic investigation of this group in future research.

ACUTE CARDIORENAL PREVENTION

In addition, quality of life change measures should include controlling DM and hypertension, stopping smoking, reducing weight, exercising regularly, and following up with cardiology for any cardiac illness, nephrology for kidney diseases, and other specialties for any other chronic diseases. Avoid unnecessary medication (nonsteroidal) and investigations such as contrast investigation. Collaborative specialized teamwork is advised to follow patients with CRS at home and in the hospital.

CONCLUSIONS

aCRS is the most common type of cardiorenal syndrome. It has a poor prognosis and a high mortality rate. Early diagnosis and treatment are essential for preventing adverse outcomes. However, the clinical presentation and available biomarkers are not specific. Although different pathophysiological mechanisms have been proposed, we believe that other mechanisms require further exploration. The prevention and treatment of AHF are the leading players in the prevention of aCRS. Achieving these targets requires comprehensive, specialized, and collaborative teamwork. There are many missing concepts in pathophysiology, biomarkers, treatment strategies, such as anti-inflammatory therapies, and a

consensus of AKI definition that requires hard work and research projects, as indicated in each section.

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