Yemen Journal of Medicine

https://yemenjmed.com

Article information

DOI: 10.63475/yjm.v5i2.0433

Article history:
Received: 02 June 2026
Accepted: 02 July 2026
Published: 20 July 2026

Correspondence to:
Elmukhtar Habas
Email: Habas1962@gmail.com
ORCID: 0000-0002-7730-9618

How to cite this article
Habas E, Rayani A, Habas A, Alarabi K, Habas E, Baghi M, et al. Cardio-reno-cardiac syndrome, classification, pathophysiology and clinical implications: Review–Part 6. Yemen J Med. Published online July 20, 2026. doi: 10.63475/yjm.v5i2.0433:1-23.

Review Article

Cardio-Reno-Cardiac Syndrome, Classification, Pathophysiology and Clinical Implications: Review–Part 6

Elmukhtar Habas[1], Amnna Rayani[2], Ala Habas[3], Kaled Alarabi[4], Eshrak Habas[5], Mohamed Baghi[4], Aml Habas[6], Mehdi Errayes[1]

1 Senior Consultant, Hamad Medical Corporation, Hamad General Hospital, Qatar University, Doha, Qatar
2 Senior Consultant, University of Tripoli, Tripoli, Libya
3 Resident, Gourtouba Dialysis Center, Open Libyan University, Tripoli, Libya
4 Associated Consultant, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar
5 Resident, TUH, University of Tripoli, Tripoli, Libya
6 Specialist, Open Libyan University, Tripoli, Libya

ABSTRACT

Type 5 cardio-renal syndrome (CRS), cardio-reno-cardiac syndrome (CRCS), is a condition secondary to systemic diseases that usually leads to acute or chronic dysfunction of the heart or kidney, which causes dysfunction of the other organ. Different pathophysiological mechanisms and factors affecting CRCS development, such as systemic lupus, hypertension, and diabetes, lead to acute and chronic damage to the heart and kidneys at the same time. Furthermore, other diseases such as hepatic cirrhosis can cause kidney failure and inapparent or apparent heart dysfunction, precipitating CRCS. In this part of the CRS review series, pathophysiology, risk factors, and management of CRCS are comprehensively reviewed, incorporating the latest evidence and recent advances in the field.

Key words: Cardiorenal syndrome, secondary CRS, cardio-reno-cardiac syndrome, sepsis, acute kidney injury, HRS, lupus nephritis, CRCS therapy

INTRODUCTION

Cardio-renal syndrome (CRS) is a well-acknowledged medical condition that describes the close relationship between heart and kidney dysfunction, where any abnormalities in one organ immediately lead to the worsening of the other. [1] CRS primarily encompasses five types that affect the heart and the kidneys. These types include a disruption in one main organ, which then triggers a disruption in its secondary organ counterpart, either chronically or acutely. [2] CRS type 5 is characterized as a secondary illness condition, namely uncontrolled hypertension, that has harmful consequences on both the heart and kidneys. [3,4] Type 5 is also known as secondary CRS. Type 5 is "systemic conditions causing simultaneous injury and/or cardiac and renal dysfunction" (e.g., sepsis, systemic lupus erythematosus [SLE], amyloidosis); however, we believe it is better known as cardio-reno-cardiac syndrome (CRCS).

CRS type 5 is characterized as a "secondary" cardiorenal syndrome, in which a systemic condition leads to simultaneous injury and/or dysfunction of the heart and kidneys (e.g., sepsis, SLE, amyloidosis, cirrhosis, and other systemic inflammatory or metabolic disorders). [4–6] In the original Acute Dialysis Quality Initiative (ADQI) consensus classification, CRS comprises five subtypes, with Type 5 specifically denoting

systemic conditions that cause concurrent cardiac and renal dysfunction. [7] More recently, a 2021 proposal in the literature suggested subdividing secondary CRS into acute secondary CRS (retaining Type 5) and a chronic secondary CRS category labeled "Type 6" (proposed construct; not yet ratified by international consensus). In this review, we use the term CRCS to emphasize the bidirectional and simultaneous nature of secondary CRS and to discuss both the ADQI Type 5 framework and the proposed chronic secondary (Type 6) concept where relevant. [8]

The kidneys and heart are often damaged by proinflammatory cytokines, complement factors, and renin-angiotensin-aldosterone system (RAAS) activation, which are typical final routes for several types of CRS. In sepsis, increased renal vascular resistance and an initial surge in proinflammatory cytokines (interleukin-6 [IL-6]) and oxidative stress might result in organ damage. [9] Sepsis leads to autonomic nervous system (ANS) dysfunction and RAAS activation. The wide range of effects of sepsis on the functioning of different organs, such as the heart and kidneys, creates a challenge in distinguishing between the direct effects of sepsis and the effects of communication across organs. Furthermore, sepsis therapy may affect the chronic cardio-renal-cardiac syndrome (CCRCS) recurrence rate. Fluid resuscitation may be needed; however, it may lead to fluid accumulation in tissues, causing swelling and resulting in increased venous congestion and decreased renal blood flow (RBF). Iodinated contrast substances and certain medications may cause cardiac damage and nephrotoxicity, leading to the development or exacerbation of CRCS. In autoimmune and chronic inflammatory diseases, the simultaneous harm to organs and continued communication between the kidneys and heart result in similar pathophysiological mechanisms, as shown in other forms of CRS. [2] Therapy mainly depends on prevention, and when it starts, controlling the precipitating cause and handling acute or chronic kidney and heart malfunction are vital therapeutic issues. The objective of this review is to delve further into CRCS by focusing on its pathophysiology, identification, and treatment to enhance the immediate detection and thereby improve the overall outcomes. An extensive search for articles published between January 2018 and December 2025 in Google, Google Scholar, EMBASE, Scopus, and PubMed was conducted using different phrases and texts, such as Renocardiac syndrome, cardiorenal syndrome, acute and chronic Renocardiac syndrome, chronic cardiorenal syndrome, type 5 and 6 cardiorenal syndrome.

CRCS TYPES AND CAUSES

CRS was defined and divided into five subtypes. [10] CRS increases mortality and morbidity, regardless of initial organ failure (heart failure [HF] leading to kidney damage or renal failure causing heart disease). CRCS is a new clinical condition for which epidemiological data are inadequate. Similar to other CRS types, CRCS (secondary CRS) was classified as acute cardio-reno-cardiac syndrome (ACRCS) and CCRCS. [8] The ACRCS is less common than the CCRCS. [8] ACRCS is usually associated with severe sepsis, while CCRCS is associated with chronic medical conditions such as diabetes mellitus (DM), hypertension, vasculitis, and congenital diseases. Recently, some authors have proposed describing acute secondary CRCS as Type 5 CRS and chronic secondary CRCS as a provisional Type 6 CRS, thereby proposing an expansion of the traditional ADQI five-type CRS framework. [8] This six-type model remains an emerging classification proposal, not a universally accepted revision, and should be interpreted with appropriate caution in clinical and research contexts.

Figure 1 summarizes the classification and etiology of CRCS.

ACRCS PATHOGENESIS

In type 5 CRS (ACRCS), acute HF or acute kidney injury (AKI) induces AKI or acute HF, respectively, and acute sepsis or acute septic shock are the main inducing conditions that precipitate ACRCS.

Pathogenesis and Predisposing Factors

The pathophysiology of CCRS is determined by specific medical conditions, duration of its development, and the circumstances in which it occurs. ACCRS is caused by systemic factors, including sepsis, medications, poisons, and connective tissue diseases, such as lupus, sarcoidosis, and Wegener's granulomatosis.

Sepsis-induced ACRCS is an acute and severe illness that significantly affects both the kidneys and heart, resulting in apparent clinical symptoms. In contrast, in cirrhotic liver illness, CRCS has a gradual and hidden start, with renal and HF progressing slowly until a critical moment is reached, and complete decompensation of both organs ensues. Multiple variables affect the CRCS trajectory. The underlying state of the kidney and heart influences the triggering events and immune and physiological responses. While the processes involved in ACRCS and CCRCS may vary to some extent, the type, intensity, and duration of organ dysfunction are also affected by the treatment provided to manage the illness. [2]

Understanding the primary causes of CRCS and identifying potential treatments requires analyzing the sequential development of the condition and the underlying illness therapy. ACRCS occurs within a specific time range that includes hyperacute (0–72 hours after diagnosis), acute (3–7 days), subacute (7–30 days), and chronic (>30 days) stages—a staging framework adapted from sepsis and AKI literature. [11–14] It should be noted that this temporal classification has not been formally validated in dedicated CRCS cohorts and represents the authors' conceptual adaptation pending prospective confirmation. Most human literature focuses on the hyperacute stage, as this has been the primary focus of interventional clinical studies undertaken in sepsis. CRCS, such as that in individuals with cirrhosis, also exhibits clear stages of pre-ascites and diuresis. Patients may have ascites that are unresponsive to diuretic treatment and persist even before the onset of hepatorenal syndrome (HRS). Typically, a specific event that raises awareness about the disease triggers CCRCS. Spontaneous bacterial peritonitis is a common complication in patients with cirrhosis. Therefore, a severe CRCS might overlap with a long-lasting, slow cirrhosis process. [15]

Direct Effects of Underlying Disorder on the Heart and Kidney

A fundamental characteristic of sepsis is the disconnection between the general blood circulation and the small blood vessel circulation in different organs, especially during the

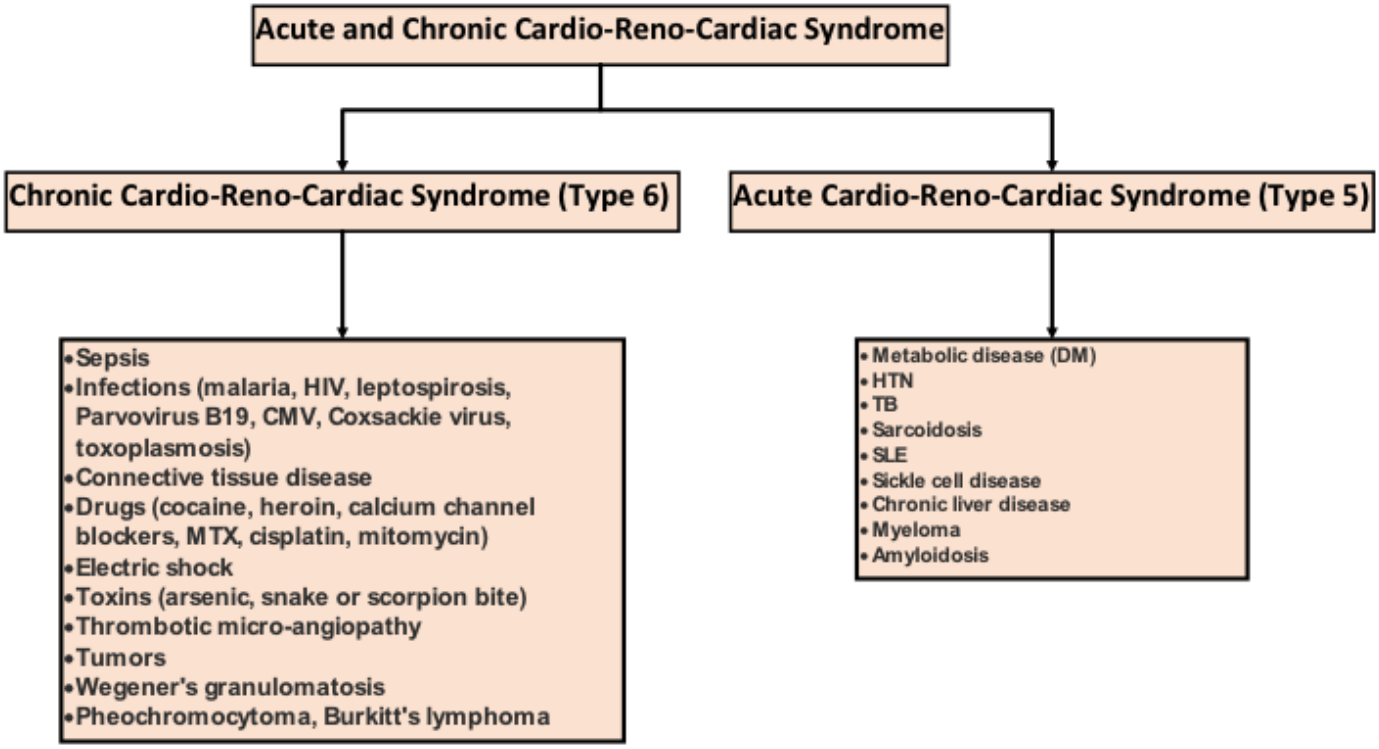

Figure 1: Classification and etiology of cardio-renal-cardiac syndrome. This diagram illustrates the two main clinical manifestations of cardio-reno-cardiac syndrome (CRCS; secondary cardiorenal syndrome) and its several underlying etiologies. CRCS is categorized according to the progression of illness into acute CRCS (ACRCS) and chronic CRCS (CCRCS). Type 6 cardio-renal syndrome (CRS) terminology reflects a proposed expansion of secondary CRS into acute (Type 5) and chronic (proposed Type 6) forms and is not part of the original Acute Dialysis Quality Initiative five-type classification. The left panel enumerates the prevalent triggers for Acute CRCS, which are often intense, temporally constrained systemic insults. These include acute infections such as sepsis and tuberculosis (TB), acute exacerbations of autoimmune disorders like systemic lupus erythematosus (SLE), and direct organ damage resulting from medication toxicity (e.g., methotrexate [MTX] or chemotherapy) or toxins. The right panel delineates the etiologies of Chronic CRCS, characterized by insidious, protracted systemic illnesses that progressively result in fibrosis and organ failure. This encompasses chronic metabolic and vascular disorders (diabetes mellitus [DM], hypertension [HTN]), persistent viral infections (hepatitis B/C, cytomegalovirus [CMV], human immunodeficiency virus [HIV]), storage disorders (Fabry disease, amyloidosis), chronic autoimmune diseases (SLE, sarcoidosis), and terminal liver disease (cirrhosis).

early stages. [16,17] Significant microcirculatory alterations may occur in the initial stages of sepsis, even if the overall systemic hemodynamics appear normal. [16,18,19] Microcirculatory alterations, such as reduced blood flow (BF) velocities and varied perfusion patterns, have a substantial correlation with rates of morbidity and death. [20]

Septic-associated cardiomyopathy (SACM) refers to the heart damage caused by sepsis. SACM is a significant factor in predicting sepsis morbidity and mortality, affecting about half of all septic patients. [21–23] Sepsis can impair and enlarge the right and left ventricles, thereby reducing their ejection fractions. This makes fluid and catecholamine therapy less effective. [24] While SACM may reach a level of severity that resembles cardiogenic shock, it typically resolves within 7 to 10 days in most patients. [21,22] Furthermore, after hypovolemia is addressed, tachycardia and decreased vascular tone enable sustained or potentially elevated cardiac output (CO) in several individuals. Despite early beliefs that state myocardial BF or energy metabolism does not impact SACM. [25] Conversely, myocardial depressants, like proinflammatory cytokines and complement factors, have been identified as significant contributors to the development of SACM. [26–28]

Neurogenic and Endocrine Alterations

Sepsis influences the central and endocrine pathways. The ANS, hypothalamus-pituitary-adrenal (HPA) axis, and RAAS alteration impair the heart and kidney function. [9]

It was reported that sepsis induces disruption in the ANS, [29,30] and the extent of ANS dysfunction is directly related to morbidity and mortality rates. [9] One characteristic of ANS dysfunction in sepsis is a decline in heart rate variability. Sepsis is linked to a reduction or complete absence of heart rate variability, which is caused by the production of inflammatory substances, such as interleukin (IL)-6, 10, and C-reactive protein. Information regarding alterations in the ANS concerning kidney function during sepsis is now restricted to animal research. However, in a study of toxic-shocked sheep, it was observed that alterations in renal sympathetic nerve activity due to sepsis did not seem to have an impact on RBF. [31]

Sepsis triggers RAAS, and RAAS activation is the body's response to restore and maintain adequate blood pressure. Despite seemingly contradictory results, new experimental and limited clinical evidence indicate that inhibiting RAAS might have positive effects. This is because RAAS activation is linked to endothelial dysfunction, organ failure, and even death in severe sepsis. [32,33] Additional experimental investigations provide additional evidence of the harmful impact of RAAS activation on kidney function in cases of sepsis. [34–36] Administering angiotensin-converting enzyme inhibitor (ACEi) enhances creatinine clearance and increases urine production in experimental bacteremia. Administering a selective angiotensin II type 1 receptor antagonist improves the flow of blood to the kidneys and increases oxygen levels in investigational endotoxemia. [9]

Sepsis induces intricate changes in the hypothalamic-pituitary-adrenal axis and glucocorticoid signaling, resulting in profound adrenal insufficiency in some individuals. [37] Adrenal insufficiency also leads to prostaglandin synthesis and increases the levels of proinflammatory factors and cytokines. It reduces adhesion molecule expression and inhibits chemotaxis. Administering glucocorticoids at a reasonable dosage for 7 days might decrease the need for vasopressors and the length of admission in the intensive care unit. [38] However, there is a lack of reliable evidence suggesting the effect of adrenal insufficiency on renal function.

AKI may aggravate sepsis-induced renal damage, causing fluid overload leading to HF and contributing to metabolic acidosis, which aggravates impaired heart function. [9] Furthermore, there is evidence proposing that AKI may have cardio-depressing effects via distantly activating pro-apoptotic and proinflammatory pathways. [39]

Additional processes and molecular pathways, including oxidative stress, inflammation, and dysregulation of the neuroendocrine regulatory system, such as vasopressin hormone, have been anticipated to contribute to CRCS pathophysiology. A systematic analysis of 637 patients from 15 studies reported a negative effect of combined cardiac and renal involvement on COVID-19 prognosis. [40] However, this body of evidence carries important methodological limitations: studies were predominantly observational, definitions of CRS varied across cohorts, and selection bias in pandemic-era populations was substantial. The observation that viral infection may exert cytotoxic effects on renal and cardiac cells—via Angiotensin-Converting Enzyme 2 (ACE2)-mediated entry and Systemic Inflammatory Response Syndrome (SIRS)-related pathways—is biologically plausible but not yet conclusively established in controlled experimental models. These findings should therefore be regarded as hypothesis-generating rather than definitive, and COVID-19-associated CRCS warrants a dedicated prospective study using standardized CRS definitions. Kidney and cardiac complications and synchronized cardiac and renal problems had a significant influence on the illness severity and the death rate in individuals with COVID-19 infection. [40]

Moreover, the hemodynamic impact of a failing heart on renal circulation, as well as cardiac alterations caused by the reduced ability of the kidney to excrete fluid, is also a problem. Nevertheless, experimental evidence has firmly demonstrated that AKI may result in impaired function of distant organs. [41] In a mouse model, AKI resulted in reduced cardiac contractility and programmed cell death (apoptosis), which was partly reversed by anti-tumor necrosis factor therapy. [39] AKI further resulted in ventricular hypertrophy. [42] AKI may lead to a rise in cardiac macrophages. [43] The impact of AKI on lung function has been extensively examined. This includes an elevation in microvascular permeability, impairment of endothelial cell function, and caspase-mediated apoptosis. [44] Moreover, AKI has a significant influence on the brain, which consecutively affects the overall neuroendocrine response in sepsis. [38] Despite its difficulty, this area of research holds great significance as it can reduce the high mortality rate caused by combined acute heart and kidney failure. There has been a slight advancement in the use of extracorporeal support devices that can remove harmful circulating factors responsible for detrimental communication between organs. However, this technology must be investigated and evaluated, particularly for humans.

Cellular and Molecular Mechanisms

In sepsis, concurrent acute heart and renal failure, and significant cellular and molecular alterations occur in both organs. A significant time-dependent pattern exists for changes in sepsis and other systemic diseases. However, this element has not yet been thoroughly investigated. In addition, it is challenging to distinguish the impact of the initial infection from the influence of organ failure unless carefully designed experimental models are used.

The activation and stimulation of cytokines, toll receptors, and leukocytes in the heart and kidney during sepsis are well recognized. [45] Macrophages, lymphocytes, neutrophils, and, more recently, T-regs have been involved in this process. A growing body of information supports the significance of danger- and pattern-associated receptors, including damage-associated molecular pattern molecules (DAMPs) and pathogen-associated molecular patterns (PAMPs). Toll receptors are particularly essential in terms of their function in pathophysiology. [46] Aberrations in oxidative stress are crucial pathways. These include mitochondrial malfunction [47] and changes in oxidative stress enzymes, namely those regulated by the Kelch-like ECH-associated protein 1 (KEAP1) and Nuclear factor erythroid 2-related factor 2 (NRF2) pathway (cellular oxidative stress regulator) (KEAP1-NRF2) pathway, [48] which is the principal protective response to oxidative stress.

The protein expression of cardiac muscles (actin and myosin) is arranged in atypical manners in cases of sepsis. Membrane-associated proteins such as dystrophin maintain cell morphology, cardiomyocyte mechanical resilience, and transmission of contractile forces in cardiomyocytes. The levels of dystrophin and related glycoproteins are significantly decreased in septic hearts. [45] Intercalated discs serve as locations where cardiomyocytes establish connections, thereby facilitating mechanical coupling and electrical signal transmission. The presence of intercalated disc parts (connexin-43 and N-cadherin) is significantly decreased during sepsis. In addition, the junctions between the cells become separated in sepsis. In septic shock, the L-type calcium currents are diminished, playing a crucial role in heart function. [49]

After sepsis, there are distinct alterations in the nephron tubules that are primarily responsible for filtration and control of fluids and electrolytes. Lipopolysaccharide directly modifies the transport of bicarbonate via toll receptors, resulting in anomalies in urine acidification. [50] Sepsis causes a decrease in autophagy in the proximal tubule, which in turn affects proximal tubule function. [51] A PAMP-included substance Lipopolysaccharide (bacterial endotoxin) (LPS) also alters the crucial glomerular protein megalin (Proximal tubule protein uptake receptor), perhaps leading to an elevation in urinary albumin levels. [52] Possibly, the integrated pathophysiological mechanisms underlying sepsis-induced ACRCS are shown in **Figure 2**.

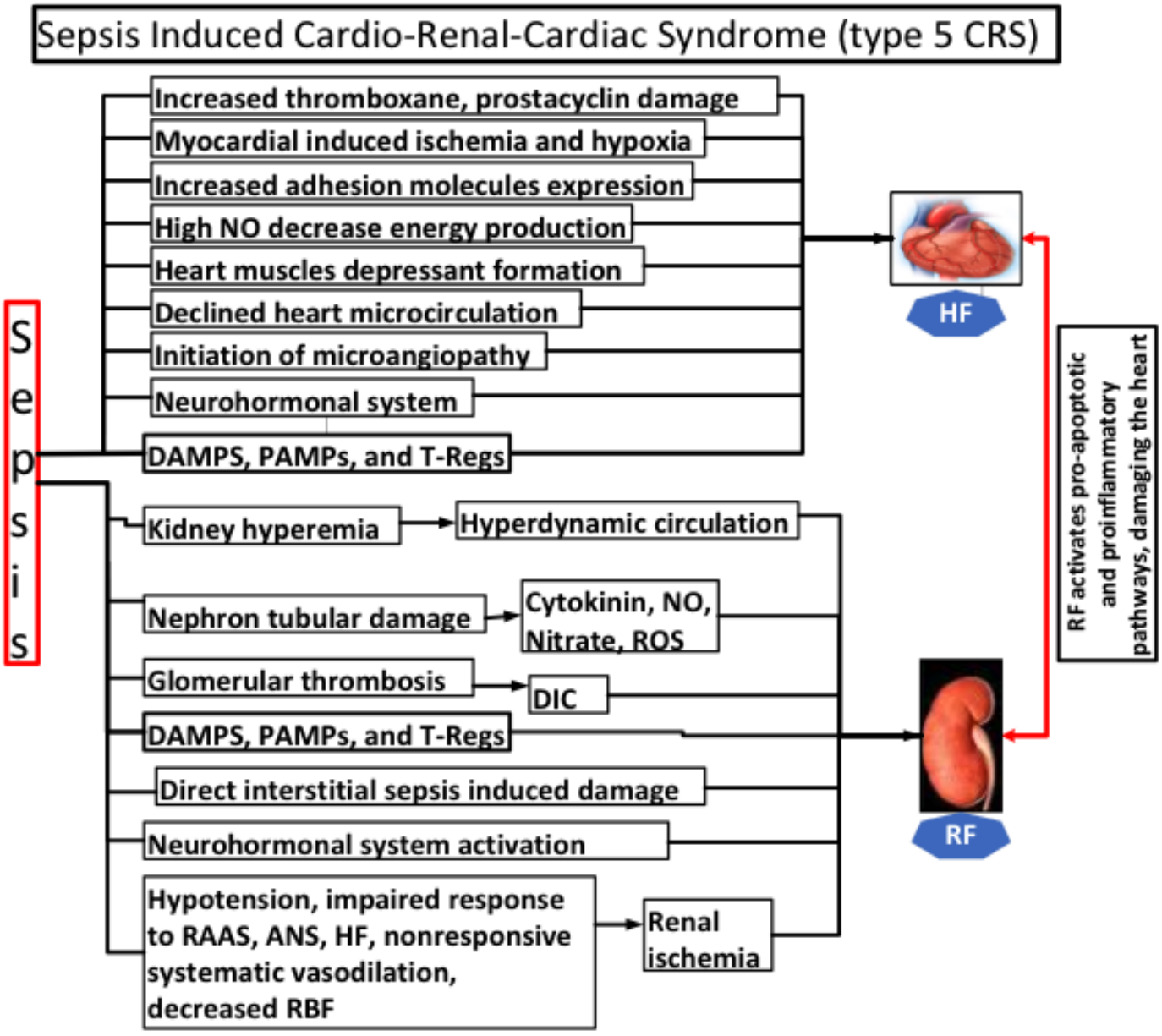

Figure 2: This image depicts the intricate interaction of systemic and organ-specific processes in sepsis that result in simultaneous heart and kidney failure. The process starts with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which activate a systemic inflammatory response. This reaction has three principal effects: 1) Direct Cellular and Molecular Injury (bottom left), including cytokine release (tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6]), oxidative stress (reactive oxygen species [ROS]), and activation of complement and leukocytes, which directly harm cardiomyocytes and tubular epithelial cells. 2) Macrocirculatory and neurohormonal dysfunction (center), characterized by autonomic nervous system (ANS) imbalance, activation of the renin-angiotensin-aldosterone system (RAAS), and systemic vasodilation, resulting in relative hypovolemia and diminished cardiac output. 3) Microcirculatory Dysfunction (right), characterized by compromised blood flow (RBF), endothelial damage, and microvascular thrombosis, resulting in tissue ischemia. These mechanisms converge to induce septic-associated cardiomyopathy (SACM) and acute kidney damage (AKI). Organ cross-talk (dotted arrows) exacerbates the cycle of failure, whereby acute kidney injury (AKI) diminishes cardiac function, and heart failure exacerbates renal perfusion.

PATHOPHYSIOLOGY OF CCRCS

CRCS (type 6CRS) is a recently recognized clinical syndrome for which comprehensive epidemiological data are incomplete. CRCS encompasses different clinical conditions, like sepsis and drug overuse, in which there is simultaneous renal and cardiac involvement secondary to an underlying pathological trigger. [16] Pathogenesis of CCRCS looks similar to ACRCS, except that the latter occurs acutely. In this section, we will discuss the pathogenesis of CCRCS in brief.

Chronic systemic diseases cause systemic inflammation, RAAS activation, sympathetic neurohormonal activation, oxidative stress, vascular endothelial dysfunction, and other pathological changes that lead to cardiac and renal fibrosis and insufficiency, producing type 6 CRS. [53,54] Type 6 CRS has overlapping and different pathophysiological mechanisms from the other types. The fibrosis pathway is exclusive to type 6 CRS and has direct implications in clinical applications and fundamental research. In animal models, elevated aldosterone levels have been shown to mediate fibrosis signaling cascades of vascular endothelial dysfunction, RAAS, and sympathetic nervous system (SNS) activation in hypertension. Neutrophil Gelatinase-Associated Lipocalin (kidney injury biomarker) (NGAL), Suppression of Tumorigenicity 2 (cardiac stress biomarker) (ST-2), aldosterone-induced fibrosis, and Galectin-3 enhance fibroblast differentiation, proliferation, and extracellular matrix protein production, thereby causing fibrosis in both organs. [55] DM causes endothelial dysfunction, chronic systemic inflammation of vessels, and oxidative stress, which promotes the transcription of inflammatory factors. The inflammatory agent transforming growth factor-beta (TGF-β), recognized for its many effects, may impact Smad transcription factors, affecting downstream signaling pathways in fibrosis. [56] Direct immunological damage in SLE promotes cardiac and renal cell apoptosis and necrosis, resulting in injury-related fibrosis. Fibrosis initially protects against systemic harm but ultimately causes heart dilatation, HF, nephron loss, and decreased estimated glomerular filtration rate (eGFR), causing type 6 cardiorenal syndrome.

The pathophysiology of CRCS is complex and disease-dependent. Connective tissue disorders, such as SLE, Wegener's granulomatosis, sarcoidosis, and others, such as sepsis, medications, and toxins, can cause ACRCS. The temporal progression of CRCS varies. Sepsis-induced ACRCS is characterized by a fulminant disease course that manifests clinically as evident clinical manifestations affecting both the kidneys and the heart, leading to acute failure of both organs. Conversely, CRCS manifests a more gradual progression in cases of cirrhosis, where renal and cardiac malfunction may develop progressively until a critical juncture is reached and complete decompensation takes place. [2] The features, classification, mechanisms, and pathophysiology of the two types of CRCS are described in **Table 1**.

Sepsis

Confirm CCRCS is used consistently here—no change needed if CCRCS is adopted as the standard abbreviation throughout. Audit all instances of CCRS and replace uniformly with CCRCS. and a precipitating event that draws attention to it. For example, cirrhotic patients are susceptible to infections that may coincide with ACRCS in chronic diseases, such as liver cirrhosis. A cardiorenal connection exists in advanced cirrhosis, which explains why these individuals exhibit altered diastolic relaxation and impaired contractile reactions to stress, in addition to splanchnic vessel dilatation and activation of vasoconstrictive systems. Potentially, altered diastolic function is a significant factor in determining kidney dysfunction and the survival of cirrhotic patients. [57]

Pathophysiological changes associated with sepsis-related CRCS result from both the systemic effects of sepsis and the direct cross-communication between the chronically injured heart and kidney. Despite normal systemic hemodynamics, microcirculation is frequently implicated in the early phases of sepsis, [18,19] correlating significantly with morbidity and death rates. Furthermore, sepsis causes cardiomyopathy, which is named SACM, which is a significant mortality predictor among septic patients. [21] Injuries to the left and right ventricles can result in dilation and a reduced ejection fraction, rendering them frequently resistant to catecholamine and fluid therapy. [24] Severe septic cardiomyopathy has the potential to resemble cardiogenic shock; however, it is typically reversible. [22,23] It appears that neither myocardial BF nor oxygen consumption is implicated in SACM pathophysiology. [25,58] There is suggestive evidence that complement factors

Table 1: Clinical, classification, and possible pathophysiological mechanisms of cardio-renal-cardiac syndrome.

Attribute	Acute CRCS	Chronic CRCS
Disease example	Sepsis	Cirrhosis
Dysfunction time	Short: hours to less than a week	Long: >30 days
Organ function	Can be on top of existing heart and renal disease	Both kidneys and the heart were adapting, then both failed progressively over time
Organ involvement sequence	It co-occurs, or the failure of both organs occurs in close timing with each other.	One organ fails, and the other organ fails after some time, e.g., cardiac dysfunction occurs before renal dysfunction in cirrhosis.
Underlying disease	The systemic event causes acute CRCS	In CCRCS, precipitating events might lead to severe worsening.
Pathophysiology	Direct effects of the cause on organs	Progressive failure of adaptive responses of both organs
Mechanisms	Decided by the underlying disease	Decided by adaptive alterations
Reversibility	This can be when the acute cause is controlled (Sepsis), and the failed organs are supported.	Very limited, except that the transplantation is conducted (liver transplant)

CCRCS, chronic cardio-renal-cardiac syndrome.

and proinflammatory mediators play pivotal roles in the SACM pathogenesis. [23,59,60]

Intra-parenchymal BF changes are evident in sepsis-associated AKI, which are distinct from systemic hemodynamic alterations associated with the septic process. [61,62] In a recent trial comparison of two distinct sepsis models, only those developing septic AKI exhibited elevated renal vasculature resistance and increases in proinflammatory cytokine (IL-6) and oxidative stress markers, regardless of systemic hemodynamic alterations. [62]

Sepsis has an independent impact on the ANS, RAAS, and HPA axis, which can affect cardiac and renal functions in multiple distinct phases. Morbidity and mortality are correlated with the severity of the dysfunction in the ANS. [30,63] The ANS dysfunction could be measured by monitoring a decrease in heart rate variability, which is frequently accompanied by the production of inflammatory biomarkers, including C-reactive protein, IL-6, and IL-10. [35] It is evident that sepsis, which involves both the heart and kidneys, induces several cellular and molecular alterations in both tissues. In animal studies, there is evidence of cytokines (TNF and IL-6) and leukocyte (neutrophils, macrophages, and lymphocytes) activation and induction in the heart and kidney. [47,48,63] Sepsis substantially impairs myocardial contractility, resulting in anomalous expression of muscle proteins (actin and myosin) and membrane-associated proteins (dystrophin). Dystrophin proteins are typically responsible for regulating cell morphology, mechanical strength, and contractility of myocardial cells. Septic myocardium involves a drop in the average quantity of dystrophin and other comparable glycoproteins. [45] Extracellular polysaccharide formation and deposition disrupt bicarbonate transport, resulting in irregularities in urine acidification and tubular injury in the kidneys caused by sepsis. [50,64] Additionally, lipopolysaccharide alters megalin, a glomerular protein that contributes to albuminuria and intrarenal inflammation, increasing and recovering normal and nephrotic albumin levels of the filtrate. [65]

Involvement of the failing heart or kidney in organ dysfunction is the most intriguing but challenging problem in multiorgan failure. Sepsis has several effects on organs, including the heart and kidneys, making it difficult to distinguish between sepsis and inter-organ crosstalk. However, sepsis-specific pathophysiology suggests specific effects of inter-organ crosstalk, including low CO, reduced renal perfusion, worsening sepsis-induced kidney dysfunction, and fluid overload from AKI, which can cause chronic HF in a dilated, hypocontractile heart. Furthermore, metabolic acidosis from AKI impairs contractility, increases heart rate, and worsens myocardial workload. The available limited experimental findings suggest that AKI depresses the heart via remotely inducing inflammatory and apoptotic pathways. [44]

In addition to hemodynamic effects on renal circulation, HF causes cardiac alterations due to impaired fluid clearance by the kidneys. Experimentally, AKI causes distant organ dysfunction. [41] AKI and lowered cardiac contractility due to apoptosis can be partly reversed by anti-TNF therapy. [66] AKI causes cardiac hypertrophy [42] and raises cardiac macrophages. [43] Moreover, AKI primarily affects the brain, which may alter the sepsis neuroendocrine response. [67] The alteration of the neuroendocrine response is interesting and needs further research, although it is one of the challenging research projects. Extracorporeal support devices that filter sepsis-circulating products, turn off the deleterious inter-organ crosstalk, and improve the outcomes of CCRCS. [9] **Figure 3** represents generalized thoughts on cardio-renal-cardiac syndrome pathophysiology.

DISEASES CAUSE CRCS

Fabry Disease

Fabry disease is a rare fat breakdown enzyme deficiency, leading to a genetic lysosomal fat deposition disorder. The fat deposits in blood vessels and tissues increase heart complications, kidney impairment and failure, and stroke. Fabry disease causes CRCS, with delayed development of kidney dysfunction and HF until decompensation. CRCS in Fabry disease may be acute, chronic, or acute-on-chronic. Fabry crises can be triggered by fever, exercise, exhaustion, stress, and abrupt temperature fluctuations, which are common reasons for CRCS development in Fabry disease. [68] As a systemic illness, Fabry's disease begins with kidney or heart injury, leading to bilateral organ crosstalk.

The ordinary course of Fabry nephropathy in adolescents remains unknown. Renal pathology worsens with age, similar to most illnesses. In patients with Fabry disease, globotriaosylceramide 3 (Gb3) deposition in the glomerular endothelium, interstitial, mesangial, and podocytes, and finally differentiated epithelial cells with many myelin-like deposits in their lysosomes, causes renal lesions. Podocyte foot process effacement is equivalent to proteinuria. The epithelium of the loop of Henle, the endothelium of renal arterioles, distal tubules, and smooth muscle cells store glycosphingolipids. [69] Renal histology shows possibly permanent alterations to glomeruli, tubules, interstitium, and vascular structures before symptoms arise. [69] By light microscopy, glomerular podocytes are inflated and finely vacuolated, similar to changes in distal tubular epithelial cells. Electron microscopy revealed lamellated lipid inclusions (zebra bodies) in the cytoplasm of the podocytes.

Clinically, the occurrence of microalbuminuria and proteinuria during 20 to 30 years of life indicates early, subtle renal impairment and may directly lead to Fabry nephropathy. Older people have worsened proteinuria. [70] Elements and fluid tubular excretion, reabsorption, and secretion. Initially, glomerular hyperfiltration may prevent renal function deterioration; however, following significant nephron damage by Gb3 deposition, renal function diminishes. Renal function declines, and azotemia usually develops between the 3rd and 5th decades. [71]

Fibrosis, tubular atrophy, and sclerosis dominate disease activity at this stage, indicating end-stage kidney disease (ESKD) in men in their 40s and 50s. Fabry disease's nephrological components cause most of its morbidity and death. Without continuous hemodialysis or kidney transplantation, patients with Fabry disease (especially men) die of uremia and ESKD.

In Fabry disease, cardiac involvement includes **c**ardiac muscle cells, valvular fibroblasts, conductive system cells, endothelial cells in all arteries, and vascular smooth muscle cells that store Gb3. [72] Gb3 storage alone cannot explain

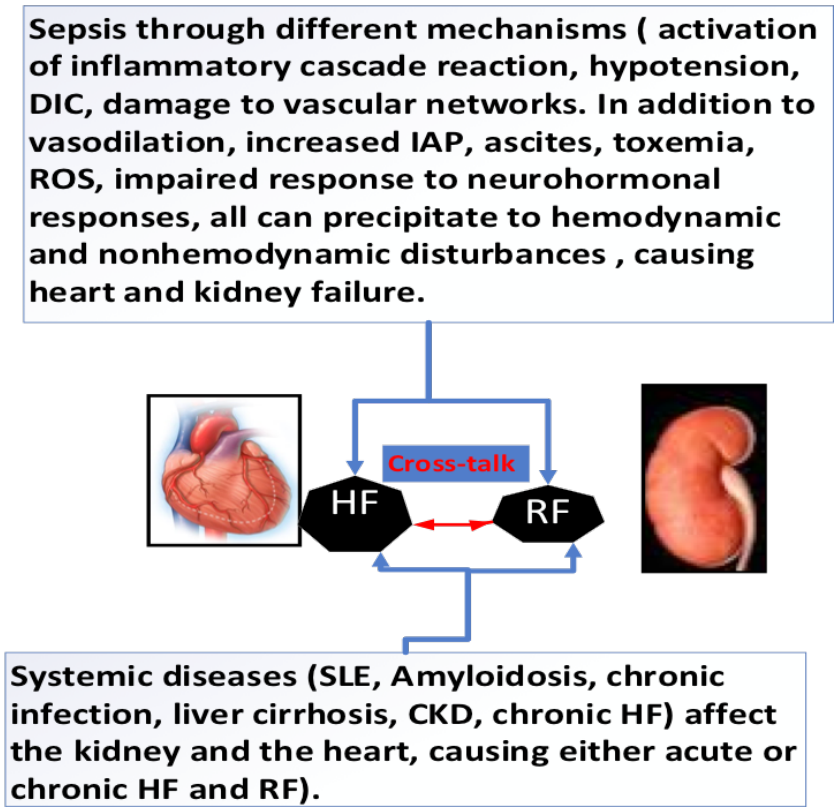

Figure 3: This image shows the intricate hemodynamic and neurohormonal cascade in advanced liver cirrhosis that results in simultaneous cardiac and renal failure, a manifestation of chronic cardio-reno-cardiac syndrome (CRCS). The process starts with liver cirrhosis (LC), resulting in structural deformation of the liver and heightened intrahepatic resistance. This results in portal hypertension, the main cause of the condition. Portal hypertension causes significant splanchnic arterial vasodilation, mostly driven by localized overproduction of nitric oxide (NO). This vasodilation sequesters blood inside the splanchnic circulation, resulting in effective central hypovolemia, characterized by a reduction in blood volume seen by the central circulation, despite potential total body fluid excess. The "underfilled" condition is identified by arterial baroreceptors, initiating a compensatory but maladaptive activation of three main neurohormonal systems (middle of figure): The sympathetic nervous system (SNS) enhances vasoconstriction of peripheral and renal arteries and increases cardiac function. The renin-angiotensin-aldosterone system (RAAS) is activated by decreased renal perfusion pressure, resulting in the secretion of renin, which subsequently induces the synthesis of angiotensin II, a strong vasoconstrictor, and aldosterone, which facilitates sodium (Na^+) and water retention. Antidiuretic hormone (ADH): Secreted by the pituitary gland (PG) in response to hemodynamic alterations, ADH facilitates the reabsorption of free water in the kidneys. Although both systems seek to normalize blood pressure, their prolonged activation has harmful effects on both target organs. Cardiac consequences (right side): The heart is required to operate against an elevated afterload (resulting from systemic vasoconstriction) and is exposed to persistent sympathetic nervous system stimulation. This leads to the progression of cirrhotic cardiomyopathy, marked by diminished contractile reserve, diastolic dysfunction, and electrophysiological irregularities, finally resulting in heart failure (HF). Renal consequences (left side): Severe renal vasoconstriction (due to the sympathetic nervous system and angiotensin II) immediately diminishes renal blood flow (RBF) and the glomerular filtration rate (GFR). This, together with salt and water retention induced by aldosterone and ADH, results in ascites and fluid overload. The extreme manifestation of this range is hepatorenal syndrome (HRS), a functional and possibly reversible kind of renal failure (RF).

the cardiac symptoms. An autopsy of a patient with Fabry disease with a severely hypertrophied heart found that only 1% to 2% of the stored material contributed to massive cardiac mass gain. Storage may cause lysosomal and cellular dysfunction, which activates various signaling pathways. Recent studies have linked metabolic and sarcomeric hypertrophic cardiomyopathies with energy deprivation. [73] In fibroblasts, energy handling in skin fibroblasts suggests Fabry disease. Magnetic resonance imaging studies of sarcomeric hypertrophic cardiomyopathies [74] have indicated an increased inorganic orthophosphate-to-ATP ratio. Left ventricular hypertrophy (LVH), angina, arrhythmia, and dyspnea occur in 40% to 60% of patients with Fabry disease. [74] Arrhythmias and reduced heart rate variability result from sinus node, conduction system, and ANS tone imbalance. Men have more severe diastolic dysfunction and nonobstructive concentric LVH than women.

Myocardial ischemia may develop from coronary vasculature dysfunction. [75] Replacement fibrosis usually begins in the mid-myocardium and posterior-lateral wall, progressing with age. [76] Eventually, transmural replacement fibrosis causes congestive HF. [77] Malignant ventricular and atrial arrhythmias associated with Fabry disease can lead to sudden cardiac death. [77] Fabry disease cardiomyopathy reduces cardiac muscle contraction and relaxation. The right ventricle had a normal cavity size and maintained systolic but poor diastolic performance, which is a characteristic feature

of Fabry disease. Fabry patients have considerably decreased myocardial perfusion reserve. [78] HF and RF usually occur in Fabry disease either together or after each other.

Amyloidosis and CRCS

Systemic amyloidosis is an uncommon condition that causes extracellular amyloid deposition in multiple organs. In amyloidosis, cardiac and renal deposition cause restrictive cardiomyopathy, and renal involvement manifests as proteinuria. The degree and presence of CRCS determine the prognosis of systemic amyloidosis. Several types of amyloidosis exist; however, primary Amyloid Light-chain amyloidosis (AL) and secondary Amyloid A amyloidosis (secondary amyloidosis) (AA) amyloidosis are the most prevalent in clinical practice. In around 50% of patients, monoclonal light chain-derived AL amyloidosis is the cause of cardiac amyloidosis. [79] Autopsy or endomyocardial biopsy revealed subclinical cardiac involvement in most cases. Kidney AL affects 30% to 40% of amyloidosis patients, [69] while 60% to 100% of AA cases involve the kidneys, and the AA cardiac involvement rate ranges between 0% and 39.5%. [80]

All four heart chambers thicken in amyloidosis, with bi-atrial dilatation, modest right ventricular dilation, and average or small left ventricular volume. Amyloid deposits and intramyocardial vascular infiltration separate myocardial cells. Sometimes, epicardial coronary arteries cause myocardial ischemia. [81,82] The conduction system is often involved, leading to conduction defects. Amyloid heart disease often causes congestive HF. Patients with modest vascular involvement and mild myocardial infiltration may manifest with angina. Cardiac arrhythmias occur, especially atrial arrhythmias. [83]

Amyloid proteins infiltrate and deposit in the glomerular basement membrane, extracellular mesangial system, and the subendothelial region. However, tubular deposits were occasionally observed. Most patients with renal amyloidosis have proteinuria, which may range from minimal asymptomatic to nephrotic range, and approximately 20% of patients present with hematuria. Patients with substantial vascular deposits might have chronic renal failure and mild proteinuria. [83] Patients with tubular deposits exhibit tubular dysfunction, which may lead to metabolic disorders (glucosuria and electrolyte abnormalities). Amyloidosis causes acute or chronic simultaneous damage and failure of both organs due to involvement of the heart and kidneys; hence, we included amyloidosis as a causative disease of CRCS (**Table 2**).

Table 2: Chronic metabolic, infiltrative, and organ-specific diseases causing cardio-renal-cardiac syndrome.

Systemic disease	Typical onset	Primary pathophysiological mechanisms	Key cardiac manifestations	Key renal manifestations	Therapeutic clues
Liver cirrhosis	Chronic with acute-on-chronic episodes	• Portal hypertension splanchnic vasodilation (NO-mediated) • Effective central hypovolemia • Maladaptive neurohormonal activation (RAAS, SNS, ADH) • Systemic inflammation • Hepatorenal axis dysfunction	• Cirrhotic cardiomyopathy • Blunted contractile reserve (inability to augment CO with stress) • Diastolic dysfunction • Electrophysiological abnormalities (prolonged QTc) • Elevated pro-BNP and troponin • Often subclinical until stress (infection, hemorrhage)	• Hepatorenal syndrome (HRS) • Renal vasoconstriction • Reduced GFR • Sodium and water retention • Ascites • Functional (potentially reversible) kidney failure	• Treat underlying liver disease • Manage complications (paracentesis, SBP, prophylaxis) • Vasoconstrictions (terlipressin, norepinephrine) + albumin for HRS • TIPS in selected patients • Avoid excessive diuresis • Liver transplantation define treatment
Diabetes mellitus (DM)	Chronic (years to decades)	• Advanced glycation end-products • Oxidative stress • Endothelial dysfunction • Chronic systemic inflammation • TGF-β mediated fibrosis • RAAS activation • Mitochondrial dysfunction	• Diabetic cardiomyopathy (independent of CAD/HTN) • LV hypertrophy • Diastolic dysfunction • Systolic dysfunction (late) • Accelerated atherosclerosis • Autonomic dysfunction	• Diabetic nephropathy • Glomerular hyperfiltration (early) • Albuminuria • Progressive GFR decline • Glomerulosclerosis • Tubulointerstitial fibrosis	• Glycemic control (SGLT2 inhibitors preferred) • RAAS blockade (ACEi/ARB) • SGLT2 inhibitors (cardiorenal protective) • GLP-1 agonis (cardiovascular benefit) • BP control • Lipid management

Hypertension (HTN)	Chronic	• Mechanic stress (pressure overload) • RAAS activation • Endothelial dysfunction • Oxidative stress • Vascular remodeling • Fibrosis (TGF-β, galectin-3 mediated)	• LV hypertrophy (concentric) • Diastolic dysfunction • Systolic dysfunction (late) • Coronary microvascular dysfunction • Atrial fibrillation • HF (HFpEF→ HFrEF)	• Hypertensive nephrosclerosis • Glomerular ischemia • Tubulointerstitial fibrosis • Progressive GFR decline • Proteinuria (usually subnephrotic)	• Strict BP control (<130/80 mm Hg) • RAAS blockade (first-line) • Calcium channel blockers • Thiazide diuretics • Combination therapy often needed
Fabry disease	Chronic (insidious, often childhood/ adolescence)	• X-linked lysosomal storage disorder • α-galactosidase A deficiency • Globotriaosylceramide (Gb3) accumulation • Cellular dysfunction and signaling pathway activation • Progressive fibrosis	• Left ventricular hypertrophy (concentric, nonobstructive) • Diastolic dysfunction • Valve involvement • Conduction abnormalities • Arrhythmias (atrial and ventricular) • Replacement fibrosis (mid-myocardium, posterolateral wall) • Reduced myocardial perfusion reserve	• Fabry nephropathy • Gb3 deposition in podocytes, glomerular, endothelium, tubule, vasculature • Proteinuria (microalbuminuria in 20s–30s) • Progressive GFR decline • Tubular dysfunction • ESRD in men by 40s–50s	• Enzyme replacement (agalsidase alpha/ beta) • Chaperone therapy (migalastat for amenable mutations) • ACEi/ARB for proteinuria • Manage arrhythmias (consider ICD) • RRT or transplantation for ESRD
Amyloidosis (AL/AA)	Chronic (progressive)	• Extracellular deposition of amyloid fibrils • AL: monoclonal light chains (plasma cell dyscrasia) • AA: serum amyloid A (chronic inflammation) • Infiltration disrupts tissue architecture and function	• Restrictive cardiomyopathy • Concentric wall thickening • Bi-atrial dilation • Diastolic dysfunction • Low-voltage ECG • Conduction defects • Angina (intramyocardial vascular infiltration) • HF (often with preserved EF)	• Proteinuria (nephrotic range common) • Progressive CKD • Glomerular basement membrane infiltration • Mesangial deposits • Tubular dysfunction (if deposits present) • Hypertension (variable)	• AL: chemotherapy (bortezomib-based), daratumumab, ASCT • AA: treat underlying inflammatory condition • Supportive care for HF (diuretics, cautions, β-blockers/ ACEi) • RRT for ESRD • Consider heart/kidney transplantation in selected patients

AA, secondary (AA) amyloidosis; ACEi, angiotensin-converting enzyme inhibitor; ADH, antidiuretic hormone; AL, primary (AL) amyloidosis; ARB, angiotensin receptor blocker; ASCT, autologous stem cell transplantation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CO, cardiac output; ECG, electrocardiogram; EF, ejection fraction; ESRD, end-stage renal disease; Gb3, globotriaosylceramide; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRS, hepatorenal syndrome; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LV, left ventricle; NO, nitric oxide; pro-BNP, pro-brain natriuretic peptide; QTc, corrected QT interval; RAAS, renin-angiotensin-aldosterone system; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SGLT2, sodium-glucose cotransporter-2; SNS, sympathetic nervous system; TGF-β, transforming growth factor-beta; TIPS, transjugular intrahepatic portosystemic shunt.

Hepatorenal and Cardio-Renal-Cardiac Syndrome (HCRCS)

Recent evidence suggests that the heart plays a substantial role in HRS, contrary to the conventional view that liver cirrhosis is the sole cause of a cascade of kidney-affecting pathophysiological mechanisms. Liver cirrhosis and renal failure may increase the risk of cirrhosis-induced cardiomyopathy in the absence of cardiac disease. Although these liver-related cardiac effects have been described clinically, heart involvement in HRS has been ignored. However, the timing of the cardiorenal interaction in HRS and

the advantageous effects of portosystemic shunting showed that the heart plays a considerable role in kidney failure in cirrhosis. Current knowledge places the liver at the core of multisystem failure-causing pathophysiological processes. [84] In HRS, the kidney-liver connection is a functional kidney failure caused by increased portal pressure and splanchnic arterial vasodilation. These lead to maladaptive neurohormonal overactivation, increased salt urine loss, and renal artery vasoconstriction, [15,84] causing kidney function decline and fluid overload. [15]

As laboratory technology improved and novel biomarkers were discovered, HRS cardiac and circulatory function monitoring became increasingly precise, [85] enhancing the concept of liver, heart, and renal involvement in CRCS. Cirrhotic cardiomyopathy may arise in HRS conditions without preexisting cardiac comorbidities due to decreased contractile reactivity to stressful stimuli and distorted diastolic relaxation with abnormalities in their electrophysiology. [86] Additionally, clinical findings suggest a molecular link between the liver, heart, and kidneys in HRS. [15]

Given how cardiac failure may mechanistically contribute to kidney dysfunction in cirrhosis, it seems sensible that cardiac dysfunction might precede HRS. [15] Cirrhotic patients who develop HRS have cardiac dysfunction features, including a decline in stroke volume before kidney function deterioration. [87] Furthermore, it was found that baseline plasma-renin activity and poor CO were the only independent predictors of HRS. [87] Interestingly, it was observed that individuals with a baseline cardiac index of < 1.5 L/min/m^2 (measured by gated myocardial perfusion imaging) were more likely to develop HRS than those with higher values. [88] Despite significant Cardiovascular Acute Kidney Injury (AKI) Classifications (CV) stress, liver transplantation does not reverse cardiac dysfunction that occurs during and after HRS. It was noted that heart performance and hemodynamics were improved post-liver transplantation. [89] These findings indicate that the heart may be involved in HRS pathophysiology and that kidney and cardiac dysfunction are not solely complications. [10,88]

Neurohormonal activation is a shared mechanism in CRS and HRS pathophysiology. [90] Many cardiac dysfunction variables, from inadequate CO to diuretic therapeutic effect, may raise neurohormone levels and harm the kidneys' function. [90] Reduced eGFR and salt and water excretion are expected. [16] Elevated right-sided heart pressure might further worsen renal hemodynamics and function by congesting the kidney venous system. [91] In the late stages of cirrhosis, moving to HRS, low CO with unchanging systemic vascular resistance drives the increased neurohormonal activity. [92] It has been demonstrated that patients with cirrhosis and acquired renal failure during spontaneous bacterial peritonitis have a lower CO than those without kidney failure. After treating spontaneous bacterial peritonitis, renal failure patients had significantly reduced CO. [88] This supports the claim that abnormalities in cardiac inotropic and chronotropic function contribute to circulatory dysfunction in HCRCS, as current evidence points to unregulated neurohormonal activation as a critical mechanism. [88,90]

Reports have suggested that increased CO causes HRS [85,93,94] because of decreased systemic vascular resistance and blood pressure. It is found that HRS is caused by an inability to increase CO during physiological stress, like in infection and hemodynamic stress, which might even be induced by dobutamine, in cirrhosis patients assessed by echocardiography. [93] Furthermore, it is reported that impaired cardiac reserve (<25% change) with low-dose dobutamine results in a 4-fold increase in HRS progression risk. [93] The use of β-blockers to increase CO may have therapeutic effects in cirrhotic patients with HRS. Further research is required to confirm this hypothesis. In established HRS-AKI, current international guidelines (European Association for the Study of the Liver; EASL) recommend terlipressin combined with albumin as first-line vasoconstrictor therapy. Terlipressin, a vasopressin analogue, reduces splanchnic vasodilation and improves renal perfusion, with the CONFIRM trial demonstrating significant improvement in HRS reversal rates compared to placebo. Albumin infusion addresses effective circulating volume depletion and exerts additional anti-inflammatory and oncotic effects. Norepinephrine combined with albumin represents an alternative in centers where terlipressin is unavailable. These therapies directly address the neurohormonal and hemodynamic derangements underlying HRS-CRCS and should be incorporated into any comprehensive management discussion.

Interestingly, despite increased CO, HRS patients had lower renal artery BF than non-HRS groups. [85] It was demonstrated that cardiac malfunction under physiological stress in cirrhosis leads to HRS. In updated consensus guidance, global longitudinal strain (GLS) is a prognostically accurate marker of systolic dysfunction in HRS subclinical myocardial dysfunction. However, there were no significant differences in GLS in HRS patients with different CO. [15,85]

During the last decade, there has been a growing interest in using serum pro-brain natriuretic peptide (pro-BNP) as a predictor of cirrhosis severity, HRS, and cirrhotic-associated cardiomyopathy. [95] A prospective observational study of 53 cirrhosis patients with 2-dimensional Doppler echocardiography and their serum troponin T and pro-BNP levels was conducted. [96] Diastolic dysfunction is common in cirrhotic individuals (56.6% in a cohort study), and serum pro-BNP and QTc levels are considerably elevated. [96] Interestingly, these patients were more likely to develop HRS, hepatic encephalopathy, and spontaneous bacterial peritonitis than those without cardiac dysfunction. [96] Despite promising results, further studies on cost-effective and clinically accurate cardiac biomarkers and imaging approaches for cirrhosis and HRS have not been conducted. The proposed mechanisms for HF and renal failure in the Health Research Classification System (HRCS) are illustrated in **Figure 3**.

Systemic Lupus Erythematosus

SLE is a multiorgan disease that simultaneously affects the kidneys and heart. Cardiac SLE involves the three heart layers (pericardium, myocardium, and endocardium), coronary vasculature, and impulse-conducting tissue.

Pericarditis symptoms are the most frequent presenting features of SLE cardiac manifestations, which can be identified in 11% to 54% of SLE patients by echocardiograms. [97] The Albumin-to-Creatinine Ratio (or Aldosterone Receptor Antagonist, depending on context) (ARA/ACR)

criteria for SLE include pericarditis. [98] The IgG and C3 deposits were granular patterns that were detected using direct immunofluorescence. Complex immune reactions are also involved in pericarditis pathogenesis. Pericardial inflammation can be acute or persistent (chronic) in its fibrinous or serofibrinous form. Pericarditis usually occurs at the outset of the illness or during relapses and seldom causes cardiac tamponade, constrictive, or purulent pericarditis. [98]

In postmortem exams, 40% of SLE patients had myocardial involvement [99] while only 20% were reported by echocardiography examination. [100] Myocardial involvement occurs in 7%-10% of cases. [101] Direct immunofluorescence shows immune complex and complement deposition, and Anti-Ro/Sjögren's Syndrome A antibodies (anti-Ro/SSA) antibodies may be associated. [102] Left ventricle failure is rare in patients with SLE-associated acute or chronic cardiomyopathy. Renal failure, hypertension, coronary cardiac disease (CAD), valvular damage, and drug toxicity used to treat SLE may cause myocardial dysfunction.

The most common endocardial involvement in SLE is Libman–Sacks endocarditis. [71] Transthoracic echocardiography reveals endocarditis in 40% to 50%, and transesophageal echocardiography reveals this valvular anomaly in 50% to 60% of SLE endocarditis. [103] Moreover, antiphospholipid antibodies stimulate endothelial cells, promoting platelet aggregation and thrombosis, causing more damage to the heart valves. [104] Additionally, immune complexes and complement deposits cause further valvular damage. Most Libman–Sacks endocarditis patients have no symptoms or signs of valvular damage. [105] Furthermore, endocardial involvement can lead to aortic valve insufficiency. Stroke and peripheral embolism occur in 13% of the patients, although these complications are uncommon.

Improved preventative strategies help patients with SLE live longer, but CV events cause more mortality and disability. CAD is 4 to 8 times higher in SLE than in other patients, and individuals of female sex are approximately 5 times more likely to develop SLE than those of male sex. [106] CAD risk factors include atherosclerosis, hypertension, arthritis, thrombosis, endocarditis, embolism, and vasospasm. [107]

In SLE patients, hypertension, sedentary lifestyle, hyperhomocysteinemia, and hyperlipidemia may cause atherosclerosis. [108] These individuals' lipoprotein and homocysteine levels rise with steroid treatment. [109] Inflammation helps in the formation of atherosclerotic plaques. Recruiting monocytes and T cells into the endothelial wall initiates atherosclerotic lesion formation. Recently, CRP and pentraxins have been regarded as inflammatory indicators in SLE. [110] Autoantibodies and immune complexes contribute to atherosclerosis. It is unknown how circulating antibodies against oxidized low-density lipoprotein (anti-OxLDL) affect the formation and progression of atherosclerosis. It was reported that OxLDL autoantibodies are more prevalent in SLE patients with CV illness than in controls or normal persons. [111]

Sinus tachycardia is the most common rhythmic abnormality in SLE patients. Anti-Ro/SSA antibodies cause atrioventricular block and bundle branch block in infants but rarely in adults. [112] These people are usually asymptomatic or experience weariness and palpitations. Rare instances include syncope. Pericarditis, myocarditis, and chloroquine usage may cause sinus tachycardia in SLE patients. [98,113]

SLE causes autoantibody formation owing to regulatory immune abnormalities. Antibodies against nuclear antigens and DNA (anti-dsDNA) are used to diagnose SLE. Anti-Sm antibodies are linked to lupus nephritis. The local binding of nuclear or other antigens to glomerular sites and in situ immune complex deposition may initiate this process. Immune complexes include DNA-anti-DNA, nucleosomes, ribosomes, chromatin, C1q, laminin, Sm, La (SS-B), Ro (SS-A), and ubiquitin, all of which cause glomerular damage. Recent findings have shown that T cells play a substantial role in the development of renal disease in SLE, not only in assisting B cells in the production of autoantibodies. In glomeruli, immune complex deposition releases chemokines such as (monocyte chemoattractant protein-1) MCP-1 and regulated on activation, normal T cell expressed and secreted (RANTES). Chemokines induce mesangial growth and cellular infiltration in acute glomerular nephritis. Chronic glomerulonephritis, interstitial fibrosis, glomerulosclerosis, and tubular atrophy may develop during the chronic phase of SLE. Toll-Like Receptor Biomarkers (Kidney and Heart) (TLR) expression on renal cells activates end-organ response and renal damage, according to recent investigations. [71]

Females are more likely to have SLE; however, both adults and children have comparable symptoms. SLE can affect any organ, including the kidneys, and it might be a presenting feature. Kidney involvement has a remission and exacerbation pattern similar to that of SLE. Usually, renal involvement is clinically present mainly due to glomerular damage. [114,115]

In 2003, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) defined renal involvement based on renal biopsy histology into five classes. [116] Class I SLE patients with solely mesangial involvement seldom develop symptomatic renal impairment. Class II patients had proteinuria of < 1 g/day. However, they have high anti-DNA antibody titers and low serum complement levels. Hypertension is rare, and the serum creatinine and GFR levels are normal. Nephrotic-range proteinuria is expected in class III patients with proteinuria of > 1 g/day. Most individuals reported hypertension and increased serum creatinine levels. Serological testing frequently reveals active lupus. Patients with class IV diffuse lupus nephritis exhibit comprehensive clinical characteristics. Most patients had proteinuria, half of whom had nephrotic proteinuria and renal impairment, which are frequently associated with hypertension. Anti-DNA antibody levels are high, and complement levels are low in these individuals. Membranous lupus nephritis (class V) causes proteinuria, edema, and other nephrotic syndrome symptoms. Of these, 40% will have less than 3 g/day of proteinuria, and up to 60% will have increased anti-DNA antibody titers and low serum complement levels. These individuals usually have hypertension and renal impairment. These class patients are prone to thromboembolic complications.

Long durations of illness flares and inactivity lead to Class VI. The patient had dormant, sclerotic, and fibrotic lesions. Hypertension and renal impairment affect most individuals. Patients' anti-DNA antibody titers and serum complement levels may normalize at this stage. [67] Hence, in SLE, all heart and kidney tissues are also involved to different degrees

according to the class or stage of SLE. The involvement of both organs occurs at a similar time, leading to their failure and producing what is known as CRCS. Management of SLE-related CRCS requires simultaneous immunosuppressive control of the underlying disease and organ-specific support. Hydroxychloroquine is recommended in all SLE patients without contraindication, given its established cardiovascular protective effects, including reduction of thrombotic risk, dyslipidemia, and disease flare frequency. For active lupus nephritis (ISN/RPS class III–V), standard induction regimens include high-dose glucocorticoids combined with mycophenolate mofetil or cyclophosphamide, as per EULAR/ERA-EDTA guidelines. Belimumab, a B-lymphocyte stimulator inhibitor, and voclosporin, a calcineurin inhibitor, have demonstrated efficacy as adjunctive therapies in lupus nephritis and should be considered where available. Concurrent cardiac manifestations—including pericarditis, myocarditis, and Libman-Sacks endocarditis—require tailored management with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or escalated immunosuppression as clinically indicated. Renal replacement therapy should be initiated according to standard AKI and CKD thresholds, without delay due to ongoing immunosuppression. **Table 3** summarizes the systemic chronic inflammatory and autoimmune diseases leading to CRCS.

Other Systemic Diseases and Therapeutic Agents Causing Cardio-Renal-Cardiac Syndrome

DM, hypertension, systemic sclerosis, rheumatoid arthritis, sarcoidosis, polyarteritis nodosa, Wegener's granulomatosis, and their therapeutic agent can cause both renal and HF and may precipitate CRCS. Malignancies such as lymphoma and chemotherapy agents can induce renal and cardiac damage, leading to failure of the heart and kidneys, precipitating CRCS. [8] **Table 4** summarizes the acute conditions that lead to CRCS.

Diagnosis of CRCS

As CRCS is clinically suspected, a systemic assessment of the involved organs is essential for therapy and prognosis. In the context of CRCS, the crucial organs are the kidneys and CV, including the heart. Nevertheless, other organs such as the brain, liver, and lungs should be considered.

Sepsis (a prototype of CRCS) diagnosis begins with sepsis and severe septic shock, followed by heart and kidney examinations, and ultimately, risk assessment to initiate therapy. Recent research has uncovered several biomarkers, including lipopolysaccharide-binding protein, C-reactive protein, procalcitonin, and proinflammatory cytokines such as IL-6 and transforming growth factor-beta, which are elevated during septic events. The results of the CRCS heart function examination were comparable to those in other myocardial dysfunction cases. Tests for natriuretic peptides and troponins are conducted to assess myocardial cell injury. CRP and leukocytosis are not exclusive to myocardial damage diagnosis; hence, doctors should choose appropriate imaging techniques.

Sepsis cardiomyopathy has a complicated etiology and clinical presentation. The early septic phase involves low-output myocardium. After fluid treatment, distributive shock with increased CO and systemic vasodilation occurs. [117] Echocardiography may reveal high-output cardiomyopathy with left ventricular regional contractility problems and left heart chamber dilatation. [118] According to Risk, Injury, Failure, Loss, End-stage renal disease (criteria for AKI) (RIFLE), Acute Kidney Injury Network (classification system) (AKIN), and Kidney Disease: Improving Global Outcomes (guidelines/criteria for AKI) Clinical Trials and Guidelines (Cardio-Renal) (KDIGO) criteria, CRCS-related sepsis kidney involvement coincides with other kinds of AKI, with a quick increase of serum creatinine and other kidney damage biomarkers. [119] The current biomarkers for kidney malfunction include cystatin C, Kidney Injury Molecule-1 (KIM-1), NGAL, and N-acetyl-beta-D-glucosaminidase (urinary enzyme marker for tubular damage) Systemic and Autoimmune Conditions (NAG); however, RIFLE, KDIGO, and AKIN guidelines still require serum creatinine levels and urine output to diagnose AKI and monitor CRCS. [71]

Systemic inflammation with a confirmed or suspected infection is vital for the diagnosis of sepsis. Shock occurs when systemic blood pressure drops severely and cannot be counteracted by physiological changes, leading to organ failure if untreated. Two or more of systemic inflammatory response syndrome criteria, which include body temperature <36°C or >38°C, heart rate >90 beats/min, tachypnea (respiratory rate >20 breaths/min), or arterial carbon dioxide partial pressure < 32 mmHg, white blood cell count < 4×10^9cells/l or >12×10^9 cells/L, or presence of >10% immature neutrophils, indicate systemic inflammation. [120] However, many sepsis studies need three of these criteria to boost diagnostic specificity. [121] The biomarkers for sepsis diagnosis and treatment response follow-up include lipopolysaccharide-binding protein and leptin. [122] procalcitonin, [123] acute phase reactants, cytokines, chemokines, and pathogen detection. [120,124]

Renal and Cardiac Function Assessment

Sepsis-induced CRCS has the same diagnostic and renal function challenges as other AKIs. The clinical cornerstone is an abrupt change in Scr; the RIFLE, [125] AKIN, [126] and KDIGO criteria describe comparable acute renal function declines. [127] These methods also assess disease severity and have advanced clinical research beyond illness detection, including risk assessment, evaluation of treatment effects, and the determination of clinically significant outcomes. Several new AKI indicators have clinical value in CRCS. [128] The biomarkers for kidney failure are discussed in Sections 1 and 2 of this review.

However, the assessment and monitoring of CRCS cardiac dysfunction involves the same methods as those used for other acute myocardial dysfunctions. Biochemical tests for natriuretic peptide and troponin showed structural alterations in the cardiac chamber and a myocyte leak. Leukocytosis and C-reactive protein levels are nonspecific for cardiac evaluation; hence, most doctors use functional monitoring. Sepsis cardiomyopathy is complicated and poorly understood, [22,23] although the early phases show a broad decrease in cardiac function resulting in inadequate CO. Fluid treatment generally causes distributive shock with fast-bounding pulses, increased CO, and systemic vasodilation. Most intensive care units no longer employ pulmonary artery catheterization for septic shock diagnosis and hemodynamic treatment, as also in CRCS. [117] The utility of echocardiography in assessing and treating intensive care unit patients with acute cardiac dysfunction is rising. [118] Even without a thorough investigation, bedside myocardial filling status and systolic function testing are adequate.

Table 3: Chronic inflammatory and autoimmune diseases causing cardio-renal-cardiac syndrome.

Systemic disease	Typical onset	Primary pathophysiological mechanisms	Key cardiac manifestations	Key renal manifestations	Therapeutic clues
Systemic Lupus Erythematosus (SLE)	• Acute flares or chronic progression	• Autoantibody formation (anti-dsDNA, anti-Sm) • Immune complex deposition • Complement activation • T-cell mediated injury • Chemokine release (MCP-1, RANTES) • Accelerated atherosclerosis	• Pericarditis (most common, 11–54%) • Myocarditis (7–10% clinical, 40% autopsy) • Libman-Sacks endocarditis (40%–60% by TEE) • Coronary artery disease (4–8× higher risk) • Conduction abnormalities • Accelerated atherosclerosis	• Lupus nephritis (ISN/RPS Classes I–VI) • Proteinuria (nephrotic to subnephrotic) • Hematuria • Hypertension • Progressive CKD • Class III/IV: most severe, active sediment • Class V: membranous, nephrotic syndrome	• Immunosuppression (corticosteroids, MMF, cyclophosphamide, belimumab) • Antimalarials (hydroxychloroquine) • Strict BP control (ACEi/ARB for proteinuria) • Manage cardiovascular risk factors • Anticoagulation if antiphospholipid syndrome
Sarcoidosis	• Acute or chronic	• Non-caseating granulomatous inflammation • T-cell mediated immune response • Cytokine dysregulation (TNF-α, IL-6) • Fibrosis (late stage) • Calcium dysregulation (1,25-OH vitamin D mediated)	• Conduction abnormalities (heart block, arrhythmias) • Ventricular tachycardia (leading cause of death) • Cardiomyopathy (regional wall motion abnormalities) • Restrictive physiology • Heart failure • Sudden cardiac death	• Granulomatous interstitial nephritis • Nephrocalcinosis (hypercalcemia) • Proteinuria (usually mild) • Progressive CKD • Glomerulonephritis (less common)	• Corticosteroids (mainstay) • Steroid-sparing agents (methotrexate, azathioprine) • Anti-TNF therapy (infliximab) for refractory disease • ICD for ventricular arrhythmias • Manage hypercalcemia • RRT for ESRD
Rheumatoid Arthritis	• Chronic	• Chronic systemic inflammation • Cytokine dysregulation (TNF-α, IL-6) • Endothelial dysfunction • Accelerated atherosclerosis • Immune complex deposition (rare)	• Accelerated atherosclerosis • Increased risk of myocardial infarction • Pericarditis • Myocarditis (rare) • Heart failure • Rheumatoid nodules (valves, conduction system)	• AA amyloidosis (secondary) • Membranous nephropathy (rare) • Mesangial proliferative GN • Drug toxicity (NSAIDs, gold, penicillamine, cyclosporine)	• Disease-modifying antirheumatic drugs (DMARDs) • Biologic agents (anti-TNF, anti-IL-6) • Manage cardiovascular risk factors • Avoid nephrotoxic NSAIDs if possible • Monitor for drug toxicity

AA, secondary (AA) amyloidosis; ACEi, angiotensin-converting enzyme inhibitor; Anti-dsDNA, anti-double-stranded deoxyribonucleic acid antibody; Anti-Sm, anti-Smith antigen antibody; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; DMARDs, disease-modifying antirheumatic drugs; ESRD, end-stage renal disease; GN, glomerulonephritis; ICD, implantable cardioverter-defibrillator; IL-6, interleukin-6; ISN/RPS, International Society of Nephrology/Renal Pathology Society; MCP-1, monocyte chemoattractant protein-1; MMF, mycophenolate mofetil; NSAIDs, nonsteroidal anti-inflammatory drugs; RANTES, regulated on activation, normal T cell expressed and secreted; RRT, renal replacement therapy; SLE, systemic lupus erythematosus; TEE, transesophageal echocardiography; TNF-α, tumor necrosis factor-alpha.

THERAPY OF CRCS

The doctor's objectives at each stage of the CRCS diagnosis must be determined. First, septic shock and severe sepsis were diagnosed, organ function was evaluated, risk was predicted, and the recommended treatment was administered. Next, improvements in organ function should be observed by utilizing physiological and biochemical changes that require attention. This is performed while stabilizing the patient and preventing organ malfunction if possible. Once a patient returns to baseline, physicians' attention should be concentrated on organ damage and long-term quality of

Table 4: Acute systemic insults causing cardio-renal-cardiac syndrome.

Systemic disease	Typical onset	Primary pathophysiological mechanisms	Key cardiac manifestations	Key renal manifestations	Therapeutic clues
Sepsis	Hyperacute to acute (hours to days)	• PAMP/DAMP release → cytokine storm (IL-6, TNF-α) • Complement activation • Microcirculatory dysfunction • Mitochondrial dysfunction, oxidative stress (ROS) • ANS imbalance, RAAS activation • Direct myocardial depression	• Sepsis-associated cardiomyopathy (SACM) • Biventricular dilation • Reduced ejection fraction • Diastolic dysfunction • Resistance to fluid and catecholamines • Usually reversible within 7–10 days	• Sepsis-associated AKI • Increased renal vascular resistance • Tubular injury (autophagy decrease, megalin downregulation) • Microvascular thrombosis • Often non-oliguric	• Source control (antibiotics, drainage) • Judicious fluid resuscitation (avoid overload) • Vasopressors (norepinephrine first-line) • Inotropes if persistent hypoperfusion • RRT if indicated • Consider immunomodulation (research)
Medications/ toxins	Acute (hours to days) or chronic	• Direct cytotoxicity • Hemodynamic alterations • Tubular injury (kidney) • Cardiomyocyte injury/apoptosis • Mitochondrial toxicity • Oxidative stress • Endothelial injury	• Chemotherapy-induced cardiomyopathy (anthracyclines, trastuzumab) • Myocarditis (immune checkpoint inhibitors) • Ischemia (5-FU, capecitabine) • Arrhythmias (tyrosine kinase inhibitors) • Heart failure	• Acute tubular injury (aminoglycosides, cisplatin, amphotericin) • Tubulointerstitial nephritis (PPIs, NSAIDs) • Glomerular injury (pamidronate, interferon) • Crystal nephropathy (methotrexate, acyclovir) • Thrombotic microangiopathy (mitomycin, gemcitabine)	• Identify and discontinue offending agent • Dose adjustment based on renal function • Hydration (e.g., for cisplatin) • Monitor cardiac and renal function • Supportive care • Consider chelation (e.g., iron in anthracycline toxicity)
Vasculitis (e.g., GPA, PAN)	Acute (flares) or chronic	• Vascular inflammation • Immune complex deposition (some types) • ANCA-mediated neutrophil activation • Endothelial injury • Thrombosis • Ischemia-reperfusion injury	• Coronary arteritis • Myocarditis • Pericarditis • Valvular involvement • Conduction abnormalities • Heart failure (ischemic or inflammatory)	• Crescentic glomerulonephritis (rapidly progressive) • Hematuria (often with red cell casts) • Proteinuria • Hypertension • Rapid GFR decline • Renal infarction (PAN)	• Immunosuppression (corticosteroids + cyclophosphamide or rituximab) • Plasma exchange for severe disease • BP control • RRT for severe AKI • Consider kidney transplantation after remission

5-FU, 5-fluorouracil; AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; ANS, autonomic nervous system; BP, blood pressure; DAMP, damage-associated molecular pattern; GPA, granulomatosis with polyangiitis; GFR, glomerular filtration rate; IL-6, interleukin-6; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMP, pathogen-associated molecular pattern; PAN, polyarteritis nodosa; PPIs, proton pump inhibitors; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; RRT, renal replacement therapy; SACM, sepsis-associated cardiomyopathy; TNF-α, tumor necrosis factor-alpha.

life implications. The strategy for CRCS therapy depends on disease modification, immune modulation, and heart and kidney support to maintain their function.

CRCS can be prevented in hyperacute sepsis by preserving hemodynamic stability, tissue perfusion, fluid management, and antibiotic therapy. Avoid fluid excess and other iatrogenic consequences by carefully managing fluid treatment (in- and output charting). [129] High-permeability membranes may remove cytokines and modulate immunomodulation, as inflammation and immunological problems cause sepsis. [130] To address heart problems, fluid therapy, vasodilators,

vasopressors, and inotropes are needed to maintain filling pressures. Vasopressors should be administered cautiously because of their low CO. Recently, levosimendan, a calcium sensitizer used to treat acute decompensated severe chronic HF has been shown to improve ejection fraction and urine volume in decompensated HF, although its usefulness in preventing CRCS is yet unknown. [129]

In chronic CRCS, particularly in the setting of HF with reduced or preserved ejection fraction coexisting with CKD, sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a cornerstone of cardiorenal protection. Large randomized controlled trials—including Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (clinical trial) (DAPA-HF), Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced), and Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE)—have demonstrated significant reductions in HF hospitalization, cardiovascular mortality, and CKD progression. Their dual cardiorenal mechanism, encompassing natriuresis, reduced intraglomerular pressure, anti-inflammatory effects, and mitochondrial protection, makes them particularly relevant to the CRCS framework. Routine consideration of SGLT2 inhibitors is recommended in stable chronic CRCS patients without contraindication, in line with current European Society of Cardiology (ESC) and KDIGO guidance. Renal support comprises removing nephrotoxic drugs and toxic media, maintaining perfusion pressure, and early dialysis if needed. [129] Therapy tactics are summarized in **Table 5**.

General Measures

In the hyperacute phase, the primary focus is on restoring and stabilizing hemodynamic variables and addressing the cause of the problem. The "Surviving Sepsis" guidelines provide advice for the early treatment of individuals with sepsis and septic shock. [117] Ensuring stable BF and sufficient oxygen supply to tissues is crucial for avoiding CRCS during the first phase. However, source control and antimicrobial coverage are also required. As previously mentioned, fluid resuscitation often leads to the buildup of fluids, and the ongoing administration of maintenance fluids may add to fluid overload, which can have harmful implications. [131] Despite fluid treatment, close control is required. Hence, it is crucial to prevent iatrogenic consequences resulting from resuscitation and promptly identify deteriorating organ function to minimize the occurrence of CRCS [9] and avoid iatrogenic fluid overloading. [132] In addition, modification of disease factors and cardiac and renal support measures can help improve the outcomes and quality of patients who survive CRCS.

Table 5: Summary of therapies for cardio-renal-cardiac syndrome.

Category	Management Strategy
General Principles	• Prevention by ensuring normal blood flow (BF) to the kidneys and heart. • Fluid resuscitation, but not excessive.
Disease Modification	• Cytokines and proinflammatory factors, interleukins, uremia, and other toxins are removed by immune modulation or renal replacement therapy (RRT).
Cardiac Support	• Maintenance of filling pressures in venous and arterial circulation components by vasodilators, vasopressors, and inotropes. • Vasoconstrictors (noradrenaline).
Renal Support	• Renal Replacement Therapy (RRT). • Fluid loss restoration. • Inotropes and vasopressors. • Systemic and intrarenal blood pressure maintenance.

Disease Modification

Molecular and pathophysiological events associated with sepsis provide numerous therapeutic targets. [21,133] The systemic inflammatory response initiated by PAMPS and DAMPS results in the synthesis and release of varied cytokines into circulation. [124,133] Physical cytokine removal and immunomodulation are two primary extracorporeal technique-based approaches that have been attempted and are currently being evaluated for disease modification. The use of adsorption achieves the removal of toxins and inflammatory end-products, [131] high-volume hemofiltration, [134] high-permeability membranes, [135,136] or convection [137] techniques, which can effectively decrease their burden. Although high-volume hemofiltration has been unsuccessful, [138] a few studies have demonstrated its potential with adsorption and high-permeability membranes. [130] Targeting cellular components of the disease response, such as neutrophil activation, apoptosis, and immune inhibition, via endotoxin removal with a polymyxin filter [139] or a citrate anticoagulant-based selective cytopheretic device is an alternative strategy. [140] Necessary trials are currently investigating these novel interventional therapies; however, small pilot studies have demonstrated the efficacy of both methods. Moreover, clinical trials of plasma filtration in conjunction with immune adsorption are currently conducted. [141,142]

Cardiac Supportive Measures

A comprehensive strategy is required to effectively manage cardiac malfunction during the hyperacute and acute stages of CRCS. This involves maintaining appropriate filling pressure by fluid resuscitation and careful administration of vasodilators, vasopressors, and inotropes. Multiple studies have assessed the impact of vasopressors on blood pressure restoration; however, they might reduce CO by increasing afterload, particularly in the presence of concurrent hypovolemia. Vasodilators enhance the ability of the heart to pump blood, particularly when its ability to contract is compromised. Norepinephrine is the most used vasoconstrictor because of its α-adrenergic activity and considerable inotropic effects resulting from its modest β-adrenergic effects. Phosphodiesterase inhibitors possess both inotropic and vasodilating actions and are anticipated to cause less of a surge in the oxygen demand of the myocardium than other inotropic drugs. Vasopressin is an effective vasoconstrictor that significantly increases arterial pressure. However, animal studies also show that it has adverse effects on CO and splanchnic perfusion. [143,144] Small and heterogeneous studies have suggested that levosimendan may offer hemodynamic benefits in decompensated HF by enhancing cardiac contractility through calcium sensitization and promoting diuresis; [144,145] However, evidence supporting its use specifically in

CRCS remains limited to observational data and pilot studies, and it cannot currently be recommended as standard therapy outside of selected clinical scenarios or trial settings. Hence, new research projects are required to ascertain whether this agent will improve CRCS patient outcomes.

Renal Supportive Measures

At present, there are no targeted pharmaceutical treatments available for kidney impairment in sepsis. [146,147] Common supportive methods are refraining from substances that might harm the kidneys, ensuring sufficient RBF, and implementing dialysis if necessary. [148] Multiple studies have assessed the impact of different vasopressor medications on enhancing renal function in sepsis. [148] Dopamine does not have a role in improving renal hemodynamics or function [143], and there have been just a few studies conducted on fenoldopam (a dopamine D1 receptor agonist). [149] In normal conditions, norepinephrine increases systemic blood pressure while reducing renal perfusion. However, in endotoxic conditions, norepinephrine increases both systemic blood pressure and renal perfusion. [150] Vasopressin, which has inherent antidiuretic properties, unexpectedly leads to a rise in urine excretion and creatinine removal in patients with septic shock. [151] The optimal goal for systemic and intrarenal blood pressure to maximize renal function is still uncertain. [152]

Management Sequence

The heart and kidneys are affected by septic shock, which presents unique difficulties. Vasopressors and inotropic support increase RBF, induce diuresis, and reduce fluid accumulation. In these situations, diuretics combined with vasopressors and inotropes produce the usual limited diuresis. [153] Hence, renal replacement therapy, like continuous renal replacement, needs further evaluation regarding the benefit of starting it at the early disease stages. [148] However, ultrafiltration at the early stage of septic shock may lead to better results. Further research is required to confirm these results. Early intervention with renal replacement therapy is also recommended to maintain acid-base balance and provide sufficient capacity for nutritional support. [9] However, the beneficial effects of renal replacement therapy need to be further investigated.

GAPS AND PROSPECTIVE

Despite advancements in characterizing CRCS, critical knowledge gaps impede optimal clinical management. These gaps span molecular mechanisms, diagnostic precision, therapeutic strategies, and population-specific considerations, necessitating a coordinated research agenda.

The pathophysiological continuum from acute sepsis-induced organ crosstalk to chronic fibrosis (e.g., via TGF-β/Smad signaling in Type 6 CRS) remains incompletely mapped. While mitochondrial dysfunction and autophagy impairment are implicated in perpetuating cardiac and renal injury, their temporal contributions and interactions require validation. Clinically, the absence of biomarkers capable of distinguishing CRCS subtypes (e.g., sepsis- vs. cirrhosis-driven) or predicting reversibility limits personalized interventions. Advanced multiorgan imaging modalities, such as simultaneous cardiac and renal magnetic resonance imaging, show promise but remain exploratory, highlighting the need for standardized protocols.

Current management of sepsis-associated CRCS lacks consensus on optimal fluid and vasopressor strategies to balance CO and renal perfusion. Similarly, immunomodulatory therapies, including cytokine removal devices and anti-fibrotic agents, demonstrate theoretical potential but lack robust long-term efficacy data. These limitations are compounded by the frequent exclusion of advanced CKD patients from large-scale randomized trials, restricting generalizability.

Pediatric CRCS and sex-based disparities (e.g., the predominance of SLE-related CRCS in individuals of female sex) are markedly understudied. Furthermore, the influence of comorbidities such as obesity and post–COVID-19 sequelae on CRCS progression remains ambiguous, underscoring the need for dedicated epidemiological studies.

Addressing these gaps demands a multidisciplinary approach. High-resolution omics technologies (proteomics, metabolomics) to elucidate organ crosstalk pathways and fibrosis drivers. Additionally, the development of subtype-specific biomarker panels and the validation of multiorgan imaging techniques. Moreover, pragmatic randomized controlled trials are needed to evaluate targeted therapies (e.g., SGLT2 inhibitors, IL-6 antagonists). Lastly, prospective cohorts are required to define pediatric CRCS phenotypes and sex-specific risk stratification models.

The proposed—and as yet non-consensus—classification of Type 6 CRS underscores shared fibrotic mechanisms, offering a preliminary framework for unified management that requires further international validation before clinical adoption. However, further refinement is needed to delineate subtypes based on oxidative stress, endothelial dysfunction, and inflammatory signatures. ACRCS, though less prevalent, warrants focused investigation into non-sepsis triggers (e.g., toxins, autoimmune flares) and novel detoxification strategies. Collaborative efforts between cardiology, nephrology, and critical care specialists are essential to translate mechanistic insights into precision therapies and improve outcomes in this high-mortality syndrome.

CONCLUSIONS

Although the pathophysiology of CRCS in acute and chronic types (types 5 and 6) is similar, clinical presentation and therapy are different. CRCS may result from several disorders of varying length and severity. Thus, linking illness to a single pathophysiological cause is complex and impossible. The time and sequence of heart and renal malfunctions depend on the cause, duration, and general health of the patient. The etiology of CRCS includes complicated heart-kidney network organ linkages and neurohormonal interactions. GFR is the gold standard for renal function, although albuminuria increases mortality, HF-related hospitalizations, and clinical, echocardiographic, and circulating congestion markers. Novel biomarkers may help us to understand the pathophysiology of AKI and cardiac disease, but their clinical roles are uncertain. Kidney ultrasonography, heart echocardiography, and other imaging techniques. Looking ahead, the clinical translation of CRCS research will depend on three parallel advances: the development and validation of subtype-specific biomarker panels capable of distinguishing sepsis-driven from cirrhosis-driven or autoimmune-driven CRCS; the design of pragmatic randomized trials that include patients with advanced

CKD and multimorbidity; and the integration of cardiology, nephrology, hepatology, and critical care expertise into unified CRCS management pathways. Recognizing CRCS as a distinct clinical entity—rather than a secondary complication of individual organ failure—is the necessary foundation for improving outcomes in this high-mortality syndrome.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

SOURCE OF FUNDING

None.

CONFLICT OF INTEREST

None.

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