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PROSPECTIVE STUDY ON THE CORRELATION BETWEEN CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR EVENTS: INSIGHTS INTO CARDIORENAL SYNDROME AND TREATMENT

Rishitha Kalchetty[1]*, Nikhilesh Andhi[2], Thupakula Rushmitha[3], Macharla Lavakumar[4], Rapher Sravani[5]

Abstract:

Background: *Cardiorenal syndrome (CRS) is characterized by the complex bidirectional interplay between the heart and kidneys, leading to acute or chronic dysfunction in either or both organs. This study aimed to investigate the correlation between chronic kidney disease (CKD) and cardiovascular events within the spectrum of CRS, focusing on the prevalence of different CRS types, the role of key risk factors and biomarkers, and the impact of combination therapies.*

Methods: *This prospective observational study enrolled patients admitted to a tertiary care center exhibiting features of CRS between November 2023 and November 2024. Patients were categorized into the five types of CRS. Data collected included demographics, medical history (hypertension, diabetes), clinical parameters, laboratory investigations (serum creatinine, NT-proBNP), and in-hospital cardiovascular events. Statistical analysis was performed using SPSS to determine the prevalence of CRS types, the association between CKD and cardiovascular events, and the influence of risk factors and biomarkers.*

Results: *A total of 396 patients were included. Chronic CRS types (II and IV) were the predominant presentations (35% and 25%, respectively), while Type III was the least prevalent (4%). Hypertension (HTN) and diabetes mellitus (DM) were major comorbidities. Mean age of the cohort was 69. Men constituted 67% of the study population. Serum creatinine and NT-proBNP were frequently elevated. Combination therapy was utilized more often than mono therapy.*

Conclusion: *Chronic CRS is prevalent in tertiary care settings. Hypertension and diabetes are significant contributing factors. NT-proBNP and serum creatinine are valuable biomarkers. Combination therapies are commonly employed, suggesting their importance in CRS management. Integrated care is crucial for optimal outcomes*

Keywords *: Cardiorenal Syndrome, Chronic Kidney Disease, Heart Failure, Biomarkers, Hypertension, Diabetes Mellitus, Combination Therapy*

Corresponding author:
Rishitha Kalchetty *,
Professor & HOD, Department of Pharmaceutics,
Hindu College of Pharmacy, Amaravathi Road,
Guntur, Andhrapradesh, India- 522002.
E-mail: drvasupharma@gmail.com

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INTRODUCTION:

The cardiorenal syndrome (CRS) represents a profound and increasingly recognized clinical entity characterized by the intricate and often devastating bidirectional interplay between the heart and kidneys. This complex interaction implies that acute or chronic dysfunction originating in one organ (either the heart or the kidney) can directly induce or significantly exacerbate dysfunction in the other, leading to a vicious cycle of progressive organ damage [Ronco C, Haapio M, House AA, et al., 2008]. This fundamental interconnectedness of the cardiovascular and renal systems necessitates a holistic approach to patient care, emphasizing the crucial importance of considering both organs in the diagnosis, risk stratification, and comprehensive management of individuals presenting with failure in either system [Epstein M, 2011]. The escalating global burden of intertwined cardiovascular disease (CVD) and chronic kidney disease (CKD) further amplifies the clinical relevance of understanding CRS.

The prevalence of CRS is substantial, affecting a significant proportion of patients with underlying heart failure and/or chronic kidney disease. Epidemiological data suggest that more than 64 million people worldwide suffer from heart failure, and a substantial proportion of these individuals, estimated between 45% and 63%, also present with concurrent renal disease [Uduman J, 2018]. This alarming co-occurrence underscores the widespread nature of CRS in clinical practice. The presence of CRS is consistently associated with significantly increased morbidity and mortality, making it a major public health concern [Hillege HL, et al., 2000]. Patients diagnosed with CRS experience higher rates of hospitalization, more frequent and severe cardiovascular events, and a markedly increased risk of all-cause and cardiovascular mortality compared to those with isolated heart or kidney disease [Anavekar NS, et al., 2004; Damman K, et al., 2011]. The economic burden associated with managing CRS patients, due to prolonged hospital stays and complex therapeutic regimens, is also considerable.

To facilitate a more precise understanding and clinical approach, CRS has been classically categorized into five distinct types based on the primary initiating event and the temporal nature of the dysfunction [Ronco C, Di Lullo L., 2017]. This classification system serves as a valuable framework for clinicians, aiding in differential diagnosis, guiding therapeutic decisions, and informing prognostic assessments.

Type 1 (Acute Cardiorenal Syndrome): Characterized by acute kidney injury (AKI) resulting from an abrupt and severe deterioration of cardiac function, such as acute decompensated heart failure or cardiogenic shock. The sudden reduction in cardiac output leads to inadequate renal perfusion, triggering compensatory mechanisms that further compromise kidney function [Nikolic T, Radovanovic M, et al., 2018; Fu K, Hu Y, Zhang H, et al., 2021].

Type 2 (Chronic Cardiorenal Syndrome): Involves chronic abnormalities in cardiac function, such as chronic congestive heart failure, leading to progressive and often irreversible chronic kidney disease. Persistent renal hypoperfusion and neurohormonal activation are key drivers in this type [De Vecchis R, Baldi C, 2014].Type 3 (Acute Renocardiac Syndrome): Defined by acute kidney injury (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction, which may manifest as heart failure, arrhythmias, or myocardial ischemia [Chuasuwan A, Kellum JA, 2012]. Systemic consequences of AKI, such as fluid overload and inflammatory mediator release, contribute to cardiac impairment.

Type 4 (Chronic Renocardiac Syndrome): Characterized by chronic kidney disease (e.g., chronic glomerular disease) contributing to chronic cardiac abnormalities, including left ventricular hypertrophy (LVH), vascular calcification, and accelerated atherosclerosis, ultimately increasing the risk of adverse cardiovascular events and reducing heart function [Clementi A, et al., 2013].Type 5 (Secondary Cardiorenal Syndrome): Refers to systemic conditions (e.g., sepsis, diabetes mellitus, systemic inflammatory diseases like lupus) that simultaneously affect both the heart and kidneys, leading to concurrent cardiac and renal failure [Di Lullo L, Ronco C, Cozzolino M, et al., 2017]. These systemic disorders promote a vicious cycle of organ failure through common pathogenic processes such as fluid imbalance, vascular alterations, and endothelial dysfunction.

The intricate pathophysiology of CRS involves a complex interplay of hemodynamic, neurohormonal, and inflammatory factors. Acute heart failure can lead to renal hypoperfusion and activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), resulting in vasoconstriction, fluid retention, and further kidney damage [Ronco C, Cicoira M, McCullough PA, 2012]. Conversely, chronic kidney disease can lead to increased uremic toxin levels, chronic inflammation, oxidative stress, and abnormalities in calcium-phosphate metabolism, all contributing to endothelial dysfunction, vascular stiffness, and accelerated atherosclerosis, thereby impacting cardiac function [House AA, 2012]. Understanding these specific mechanisms involved in each type of CRS is crucial for developing

targeted and effective therapeutic interventions.
Early detection and accurate diagnosis of CRS are paramount for improving patient prognosis. Biomarkers play a critical role in this regard, offering insights into the onset, progression, and efficacy of treatment, as well as aiding in the precise characterization of CRS subtypes [Fu K, Hu Y, Zhang H, et al., 2021]. Elevated levels of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are indicative of cardiac stress and heart failure, while serum creatinine and estimated glomerular filtration rate (eGFR) are essential for assessing renal function [Ronco C, Di Lullo L., 2017]. Other emerging biomarkers, such as troponins (indicating myocardial damage) and cystatin C (a more precise marker of kidney function), also hold significant clinical importance in CRS diagnosis and prognostication [Di Lullo L, Reeves PB, Bellasi A, Ronco C, 2019].

Despite advancements in understanding CRS, significant clinical challenges remain. The optimal management strategies, particularly for chronic forms of the syndrome, are still evolving. This prospective study aimed to address some of these gaps by investigating the clinical characteristics, prevalence of different CRS types, the role of common risk factors such as hypertension and diabetes, the utility of established biomarkers, and the impact of various treatment strategies on patients admitted to a tertiary care center. By providing real-world data from a comprehensive patient cohort, this study seeks to contribute valuable insights into the current landscape of CRS management and identify areas for future research and clinical improvement.

2. MATERIALS AND METHODS:

2.1 Study Design

This was a prospective observational study conducted at a tertiary care hospital. The study design was chosen to reflect real-world clinical practice and to capture the natural history of CRS in hospitalized patients. Observational studies, while not able to establish causality, provide valuable insights into the prevalence, clinical characteristics, and outcomes of diseases in routine clinical settings.

2.2 Study Population

Patients admitted to the hospital between November 2023 and November 2024 were screened for eligibility. The study period was chosen to allow for sufficient patient enrollment and data collection.

2.2.1 Inclusion Criteria

Patients were included if they met the following criteria: Age ≥ 30 years: This age cutoff was chosen to include the majority of adult patients with CRS. Presence of AKI, CKD, and/or cardiovascular disease (CVD): This criterion ensured that the study population included patients with evidence of both cardiac and renal dysfunction. Irrespective of gender: Both male and female patients were included to ensure generalizability of the findings. Presence of comorbidities: Patients with other medical conditions were not excluded, as comorbidities are common in patients with CRS. Patients on polypharmacy: Patients taking multiple medications were included, as this is typical in the CRS population. In-patients: Only patients admitted to the hospital were included, as the study focused on the acute management of CRS.

2.2.2 Exclusion Criteria

Patients were excluded if they met any of the following criteria: Patients not willing to consent: Informed consent is essential for ethical research. Pregnant women, lactating women, and pediatric patients: These populations were excluded due to specific physiological considerations and potential risks. Incomplete patient case sheets: Patients with insufficient data were excluded to ensure data quality.

2.3 Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (IEC) of [Please specify the name of the institution]. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants or their legal representatives prior to enrollment in the study. Patient confidentiality was maintained throughout the study.

2.4 Data Collection

Data was collected prospectively using a standardized data collection form. Trained research personnel collected the data from patient medical records and through direct patient interviews.

2.4.1 Demographics

The following demographic information was collected: Age (years), Gender (male or female)

2.4.2 Past Medical History

Detailed information on past medical history was obtained, with a focus on: Hypertension (HTN): Defined as a history of diagnosed hypertension or use of antihypertensive medications. Diabetes Mellitus (DM): Defined as a history of diagnosed diabetes mellitus or use of antidiabetic medications. Known cardiovascular disease (CVD): Including coronary artery disease, heart failure, valvular heart disease, and arrhythmias. Known kidney disease: Including CKD and other renal disorders.

2.4.3 Presenting Symptoms and Clinical Signs

The following presenting symptoms and clinical signs were recorded. Pedal edema, Chest pain, Low urine output, Shortness of breath and other relevant symptoms

2.4.4 Laboratory Investigations

The following laboratory investigations were performed at admission which include Serum creatinine (mg/dL), marker of renal function, N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/mL), marker of cardiac stress. Electrolytes (sodium, potassium, chloride) (mmol/L) to assess electrolyte balance and other relevant laboratory tests as clinically indicated.

2.4.5 Imaging Studies

The following imaging studies were performed as clinically indicated which include Echocardiography (2D Echo) to assess cardiac structure and function, Renal ultrasonography (USG Abdomen) to assess renal structure and size.

2.4.6 Treatment Strategies

Detailed information on in-hospital treatment strategies was recorded, including medications: Including cardiovascular medications (e.g., diuretics, ACE inhibitors, beta-blockers) and renal medications and Renal replacement therapy (RRT): Including hemodialysis, peritoneal dialysis, or continuous renal replacement therapy and other interventions as clinically indicated.

2.5 Classification of Cardiorenal Syndrome Types

Patients were classified into the five types of CRS based on the primary organ dysfunction leading to the syndrome, according to the established classification [Ronco C, Di Lullo L., 2017]. Type 1 (Acute Cardiorenal Syndrome): Acute cardiac dysfunction (e.g., acute decompensated heart failure, cardiogenic shock) leading to acute kidney injury,Type 2 (Chronic Cardiorenal Syndrome): Chronic cardiac abnormalities causing progressive chronic kidney disease, Type 3 (Acute Renocardiac Syndrome): Acute kidney injury causing acute cardiac dysfunction., Type 4 (Chronic Renocardiac Syndrome): Chronic kidney disease contributing to chronic cardiac abnormalities and Type 5 (Secondary Cardiorenal Syndrome): Systemic illness (e.g., sepsis, diabetes mellitus) causing simultaneous dysfunction of both the heart and kidneys.

The classification was made by the treating physicians based on a comprehensive evaluation of the patient's clinical presentation, medical history, laboratory findings, and imaging studies.

2.6 Statistical Analysis

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences

Descriptive statistics: Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means with standard deviations or medians with interquartile ranges, as appropriate. Prevalence of CRS types: The prevalence of each CRS type was calculated as the proportion of patients within each category. Comparison of groups: Chi-square tests were used to compare categorical variables between groups. T-tests or Mann-Whitney U tests were used to compare continuous variables between groups, as appropriate. Correlation analysis: Pearson's correlation was used to determine the linear relationship between continuous variables. Regression analysis: Logistic regression analysis was used to identify predictors of outcomes. P-value: A p-value of < 0.05 was considered statistically significant. Confidence intervals: 95% confidence intervals (CI) were calculated for relevant statistics.

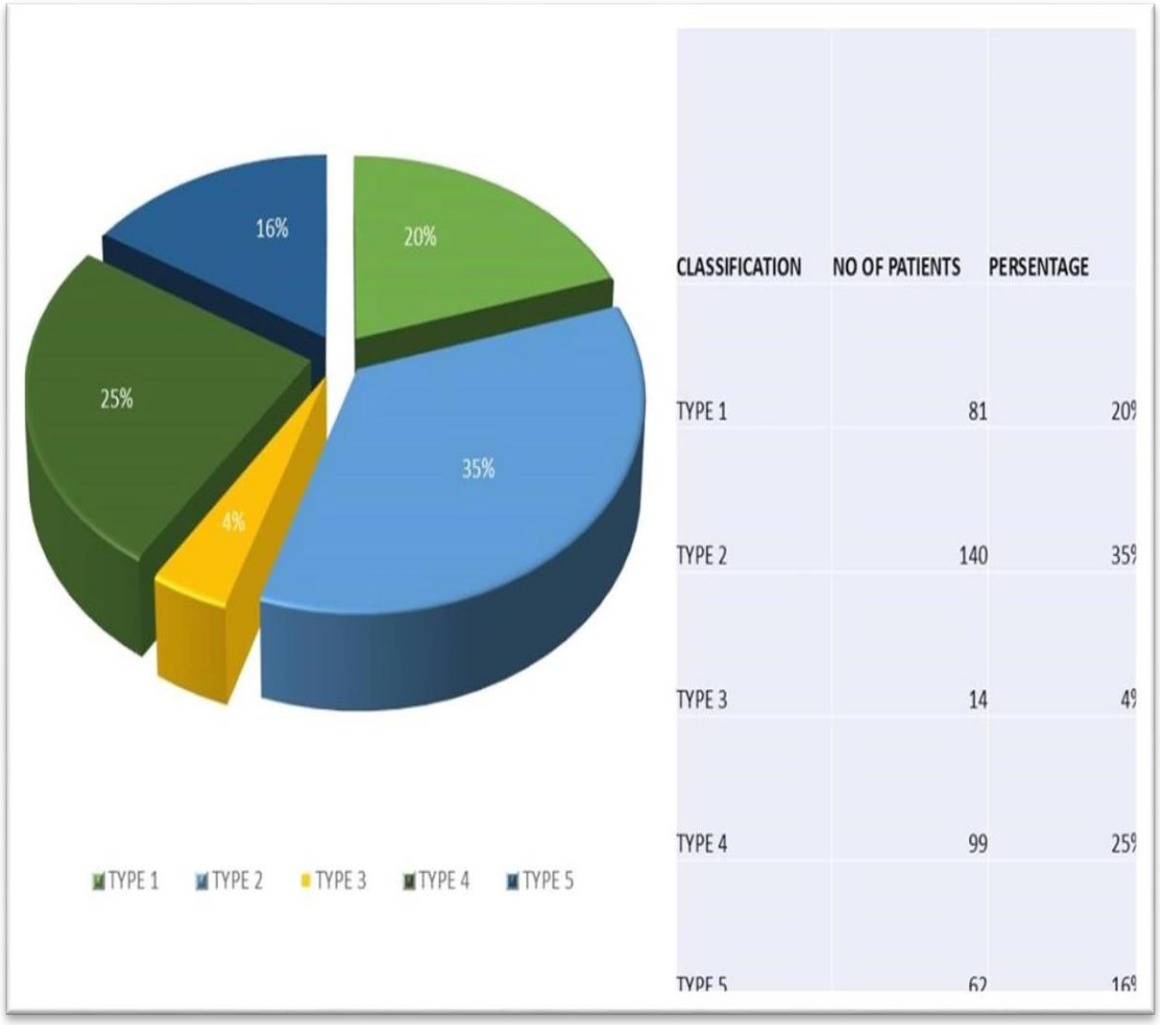
3. RESULTS :

DISEASES CLASSIFICATION:

A complicated disorder known as cardiorenal syndrome (CRS) causes the heart and kidneys to interact so that problems with one might lead to problems with the other. It is divided into five categories according to the main organ impacted and the duration of the malfunction.

Type 1 (Acute Cardiorenal Syndrome): sudden kidney damage (AKI) or a sharp reduction in renal function are caused by acute heart failure or sudden decompensation of chronic heart failure. Type 2 (chronic cardiorenal syndrome) is the cause of worsening chronic kidney disease (CKD) over time. Type 3 (Acute renal cardiac syndrome) Acute renal damage that results in acute heart dysfunction, such as heart failure, arrhythmias, or ischaemia. Type4 Heart failure, coronary artery disease, arrhythmias are examples of chronic cardiac dysfunction brought on by chronic renal disease. Type 5 (Secondary Cardiorenal Syndrome): Sepsis, diabetes, and systemic lupus erythematosus are examples of systemic illnesses that produce simultaneous failure of the kidneys and heart. These categories aid in deciphering the pathogenesis and providing direction for treating CRS patients.

Type 2 has the largest patient majority, whereas type 3 has the fewest people, as shown in Figure 1: In contrast, type 4 also has the highest possible patient count. This graph also illustrates how diseases progress from acute to chronic, such as type 1 against type 2 and type 3 versus type 4, and shows which chronic ailments see the greatest number of patients.



CLASSIFICATION	NO OF PATIENTS	PERSENTAGE
TYPE 1	81	20%
TYPE 2	140	35%
TYPE 3	14	4%
TYPE 4	99	25%
TYPE 5	62	16%

. Figure 1.0 Representation of Comorbidities among the CRS patients.

DEMOGRAPHICS:

Gender can influence the progression and outcomes of cardio renal syndrome (CRS), which is a complex condition involving the interplay between heart and kidney dysfunction. Men generally have a higher percentage (67%) of cardiovascular diseases, which can lead to cardio renal syndrome where as women (33%). Gender distribution with type 1, men with the present (56%) were viewed as women with the present (44%), and in type 2, men with the present (72%), and women with the present (28%), were seen. Regarding type 3, men are seen with (71%) while women are seen with (29%). In type 4, women have 34 percent and men have 66 percent. Similarly, in type 5, men make up the majority (70%) and women make up (30%). Results showed that in type 1, men with the present (56%) were viewed as women with the present (44%), and in type 2, men with the present (72%), and women with the present (28%), were seen. Regarding type 3, men are seen with (71%) while women are seen with (29%). In type 4, women have (34%) and men have (66%) Similarly, in type 5, men make up the majority (70%) and women make up (30%.) Men-are more likely than women to develop heart disease may progress more slowly in women, when symptoms do arise, they frequently show signs of a more advanced stage.

Age significantly impacts patients with cardio renal syndrome (CRS). Both cardiac and renal functions naturally decline with age which reduce cardiac output and glomerular filtration rate which makes the organs more susceptible to dysfunction. The baseline age grouping features for each kind of CRS are the majority of all age groups in all categories belonged to the 51–60 age group, while the age groups 41–50 & >80 had the lowest percentage. As we can see, the age group 51–60 has the highest present percentage (36%) in types 1, 2, 3, and 5. In type 4 the age range 61–70 is represented by the largest current age group (41%).

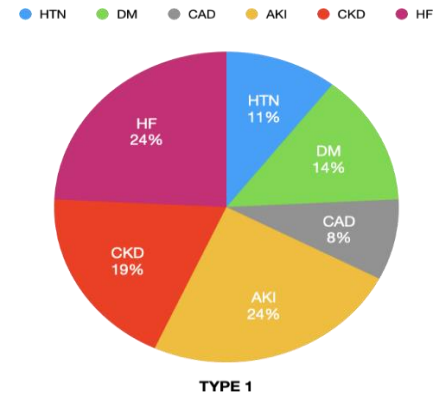
Social History: This illness can be made worse by alcohol and tobacco use. Smoking accelerates atherosclerosis (hardening of the arteries), increases blood pressure, and induces endothelial dysfunction. Smoking can also impair the kidney function by reducing blood flow to the kidneys, promoting glomerular hypertension, and increasing oxidative stress and inflammation. On other hand alcohol consumption can lead to cardiomyopathy, arrhythmia, and hypertension. Due to excessive alcohol can cause dehydration, which stresses the kidneys. Over time, alcohol can lead to hypertension and liver damage, both of which negatively impact kidney function When combined, smoking and alcohol can synergistically worsen cardiovascular 30% of patients report drinking alcohol, however 70% do not have a history of alcoholism. at the same time 10% of the patient smoke, compared to 90% of patients who do not smoke.

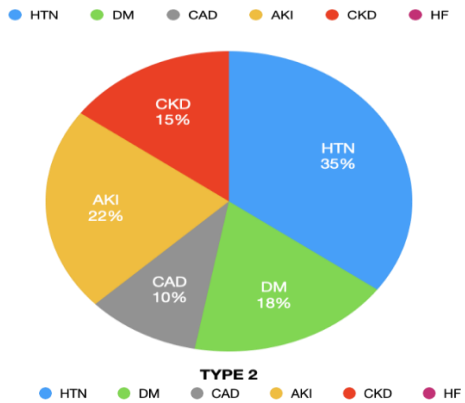
COMORBIDITIES:

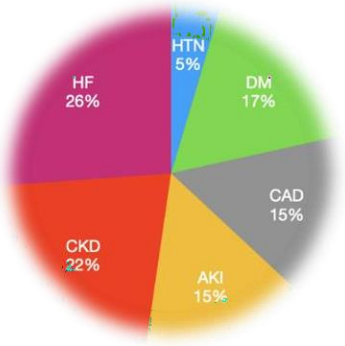
Hypertension: One of the main risk factors for kidney and heart disease, high blood pressure also plays a role in the development of CRS. *Diabetes:* Heart failure and kidney illness are closely associated with diabetes, especially type 2, which raises the risk of CRS.

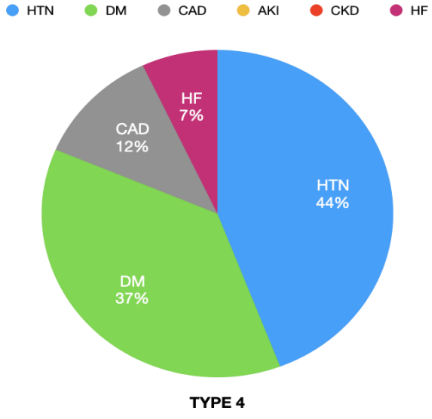
Coronary artery disease: A frequent cause of heart issues, CAD, can exacerbate CRS by lowering cardiac output, which results in renal hypoperfusion and malfunction. *Acute Kidney Injury:* CRS can result from AKI, a severe reduction in kidney function that can be brought on by conditions like sepsis or heart failure.

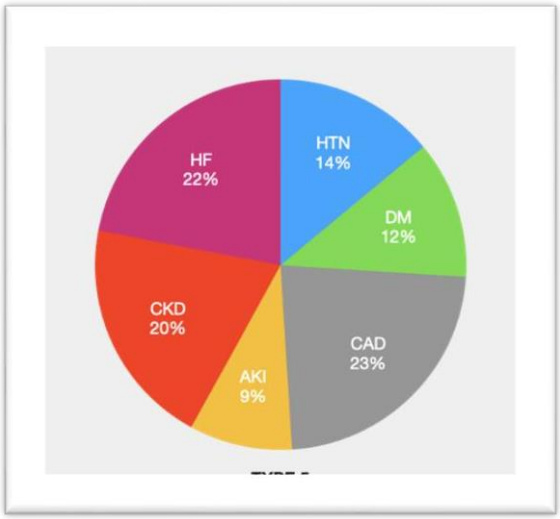
Chronic kidney disease: Both acute and chronic kidney illness can impair cardiac function and have a role in the development of CRS. *Heart failure:* Fluid accumulation and decreased blood flow to the kidneys can result from heart failure, which occurs when the heart is unable to pump blood efficiently, and renal dysfunction can follow.











DIALYSIS:

Dialysis can have several effects on patients with cardio renal syndrome (CRS), a condition characterized by the interrelated dysfunction of the heart and kidneys. Dialysis helps in managing the fluid overload, which is common in CRS patients. By removing excess fluid, dialysis can reduce the workload on the heart and help control blood pressure. Dialysis corrects imbalances in electrolytes (such as potassium and sodium), which can prevent arrhythmia and other cardiac issues. Dialysis clears waste products from the blood that the kidneys can no longer filter, reducing the risk of complications that could affect both the kidneys and heart. However, dialysis also carries risks, such as infections, vascular access complications, and potential for rapid fluid shifts that might stress the cardiovascular system. Therefore, careful management and monitoring are essential for CRS patients undergoing dialysis.

Figure 3.0 Visual representation Comparison of Dialysis patients versus Disease classification among the CRS patient

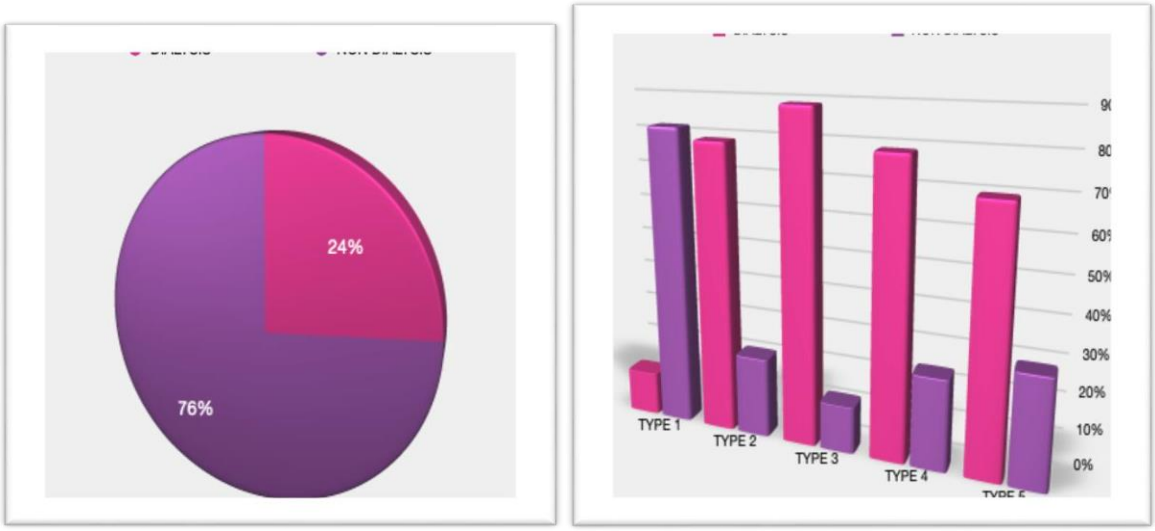


Figure 3.0 illustrates the proportion of dialysis patients with cardiac renal syndrome. Based on the graphs, it can be shown that 76% of patients do not receive dialysis, whereas (24%) do. Additionally, the graph illustrates the percentage of dialysis patients in each CRS type. As can be seen in the accompanying graph, type 5 has the highest percentage of dialysis patients (30%), while types 1 and 3 have the lowest percentage. However, there are hazards associated with dialysis as well, including the possibility of infections, issues with vascular access, and sudden changes in fluid that could strain the cardiovascular system.

FUNCTIONAL ABNORMALITIES AND STRUCTURAL ABNORMALITIES:

Heart-kidney diseases are referred to as CRS because acute or chronic failure in one organ can cause dysfunction in the other. Bidirectional Relationship: The kidneys and heart are linked by a number of routes, and problems with one organ can have an adverse effect on the other's operation.

Hemodynamic Changes: A malfunctioning heart may cause acute kidney damage (AKI) or exacerbate chronic kidney disease (CKD) by reducing blood supply to the kidneys.

Neurohormonal Activation: When heart failure strikes, the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are triggered. This can lead to water and salt retention, which deteriorates kidney function.

Inflammation and Oxidative Stress: The development and progression of CRS are influenced by oxidative stress and inflammation, which impact the tissues of the heart and kidneys.

Fibrosis: Chronic dysfunction can further decrease organ performance by causing cardiac and renal fibrosis, or scarring.

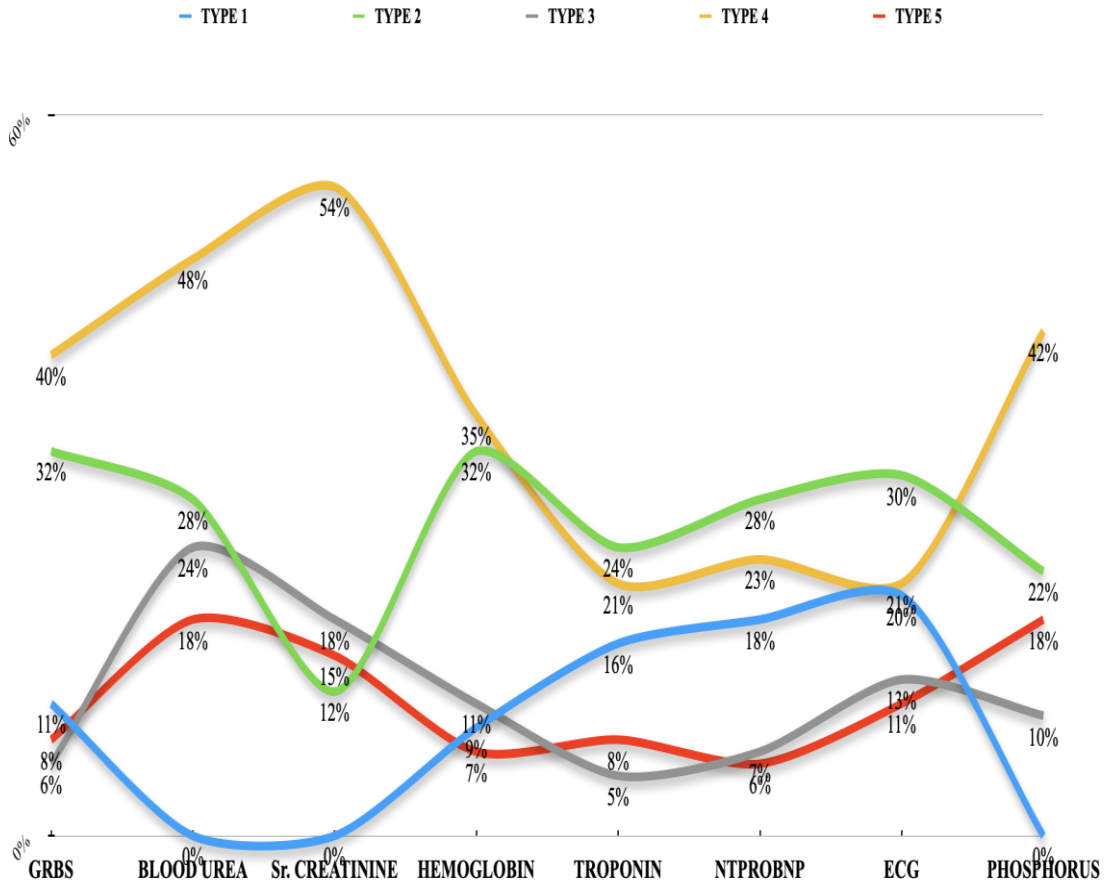


Figure 4.0 Visualization of relationship between renal & cardiac functional biomarkers with disease classification of CRS.

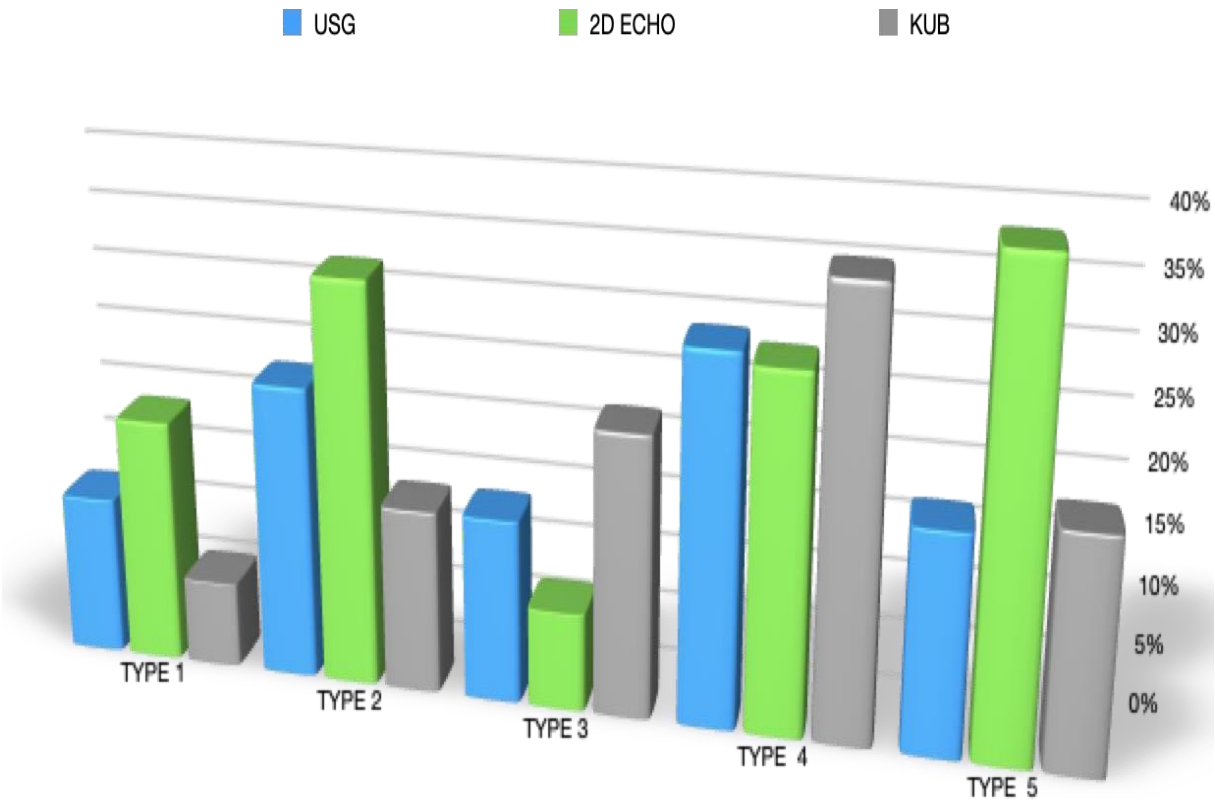


Figure: 5.0 Visualization of relationship between renal & cardiac structural biomarkers with disease classification of CRS.

DISEASE PROGRESSION:

Heart and kidney malfunction interact in both directions during the course of cardiorenal syndrome (CRS), and acute or chronic problems in one organ can cause dysfunction in the other, creating a complicated and sometimes lethal development.

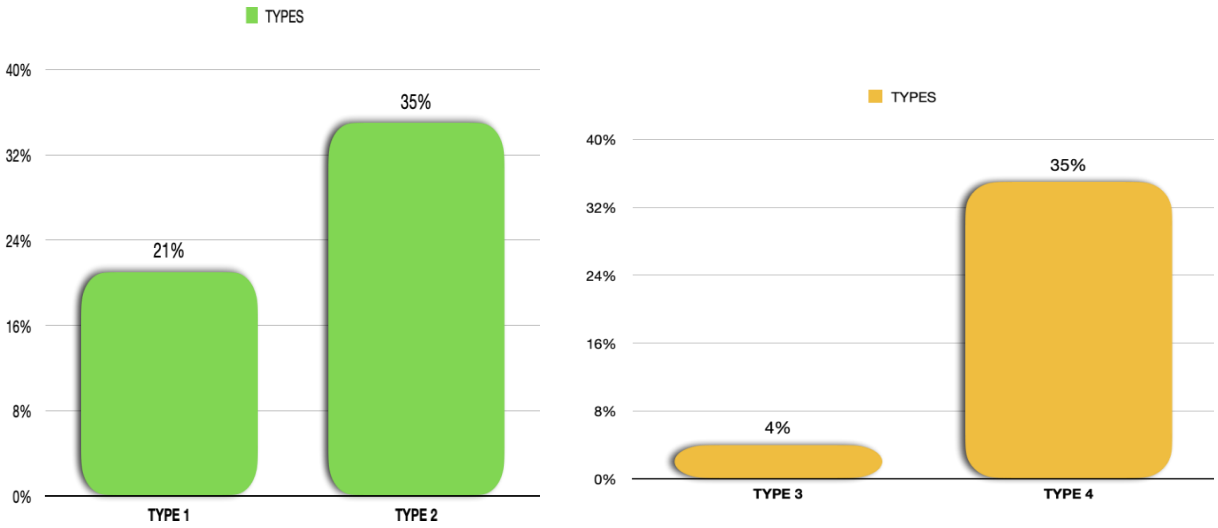


Figure 6.0 Clinical findings of Disease progression.

THERAPY:

Mono therapy involves the use of a single drug to manage CRS. This approach might be used in less severe cases or when a specific drug is known to effectively target the underlying mechanism of the disease. Mono therapy drugs include Diuretics, ACE inhibitors, ARBS, and Beta Blockers. Combinational therapy involves the use of two or more drugs with different mechanisms of action to manage CRS. This approach is often necessary in more severe cases or when mono therapy is insufficient. It includes other renal and cardiac drugs along with the mono therapy drugs. the choice between mono therapy and Combinational therapy in CRS depends on the severity of the condition, the patient's overall health, and the specific goals of treatment. It is evident from Figure 7.0 that 64% more people utilize combination therapy than mono therapy. In the CRS classification 36%. The graph indicates that combination therapy is typically more suggested than mono therapy for chronic disorders.

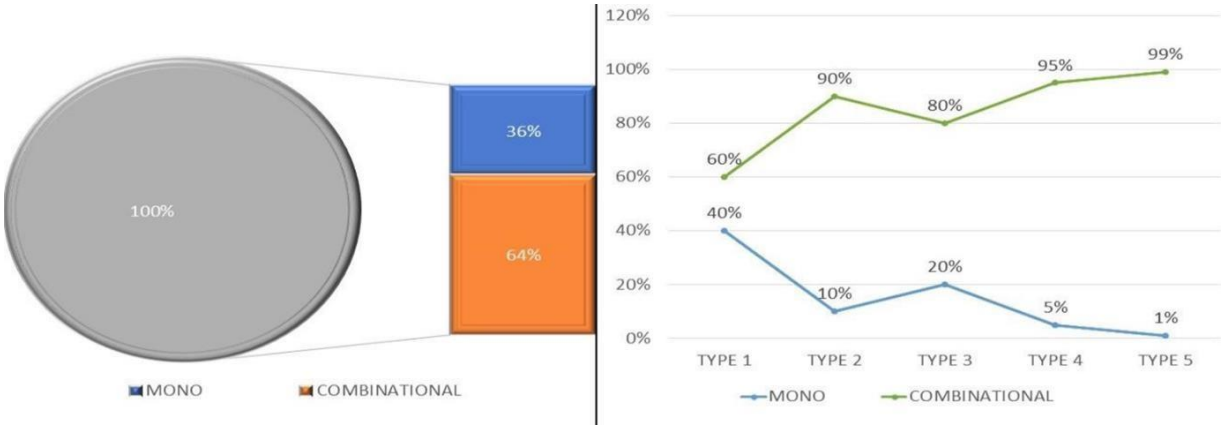


Figure 7.0 Representation of mono and Combinational therapy with type wise classification.

CARDIAC TREATMENT:

The use of cardiac drugs in cardio renal syndrome involves careful management to address both heart and kidney dysfunction the drugs used in CRS are Diuretics, Ca+ channel blockers, ACEI, ARBS, Beta blockers, Anti-platelets, Anti-coagulants, Anti-Hyper lipidemic, Anti-anginal, Anti Arrhythmia. The choice and dosage of these medications must be individualized, balancing the benefits for heart failure against the risk of worsening renal function and managing electrolyte abnormalities. Regular monitoring of kidney function and electrolytes essential to optimize treatment and minimize complications.

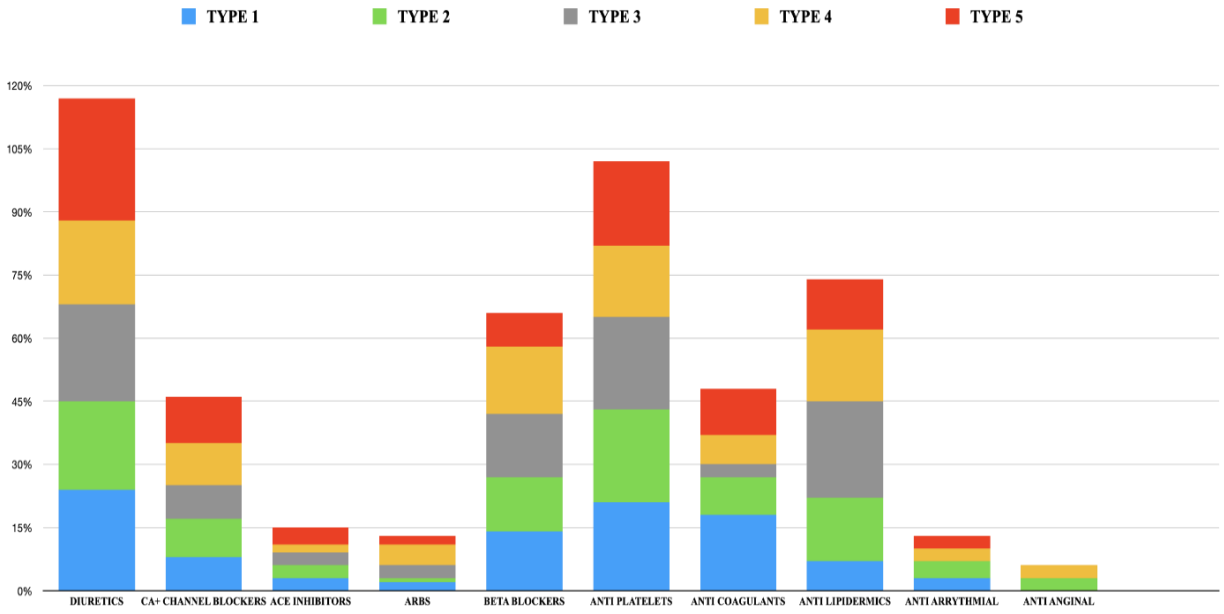


Figure 8.0 Representation of cardiac treatment with respect to CRS types.

CARDIAC DRUGS	TYPE 1	TYPE 2	TYPE 3	TYPE 4	TYPE 5
DIURETICS	24%	21%	23%	20%	29%
CA+ CHANNEL BLOCKERS	8%	9%	8%	10%	11%
ACE INHIBITORS	3%	3%	3%	2%	4%
ARBS	2%	1%	3%	5%	2%
BETA BLOCKERS	14%	13%	15%	16%	8%
ANTI PLATELETS	21%	22%	22%	17%	20%
ANTI COAGULANTS	18%	9%	3%	7%	11%
ANTI LIPIDERMICS	7%	15%	23%	17%	12%
ANTI ARRYTHMIAL	3%	4%	0%	3%	3%
ANTI ANGINAL	0%	3%	0%	3%	0%

Regarding the CRS classification, Figure 8.0 describes how cardiac medications are used. The picture shows that while anti-arrhythmia and Anti-anginal medications are less frequently used, diuretics are used in all types most frequently. Anti-platelets, Anti-lipidemic and beta blockers are also commonly used in addition to diuretics.

RENAL TREATMENT:

The use of cardiac drugs in cardio renal syndrome involves careful management to address both heart and kidney dysfunction the drugs used in CRS are Anti-diabetic, Antibiotics, K+ inhibition, Phosphate Binders, Alkalizing agents, PPI, Supplements, Vasopressin's, ESH etc. These drugs are used in all the conditions in renal patients. Regarding the CRS classification, Figure 9.0 describes how renal medications are used. The picture shows that while ESH and Vasopressin medications are less frequently used, diuretics and Antibiotics are used in all types most frequently. Anti-diabetic, supplements and, and PPI are also commonly used in addition to diuretics.

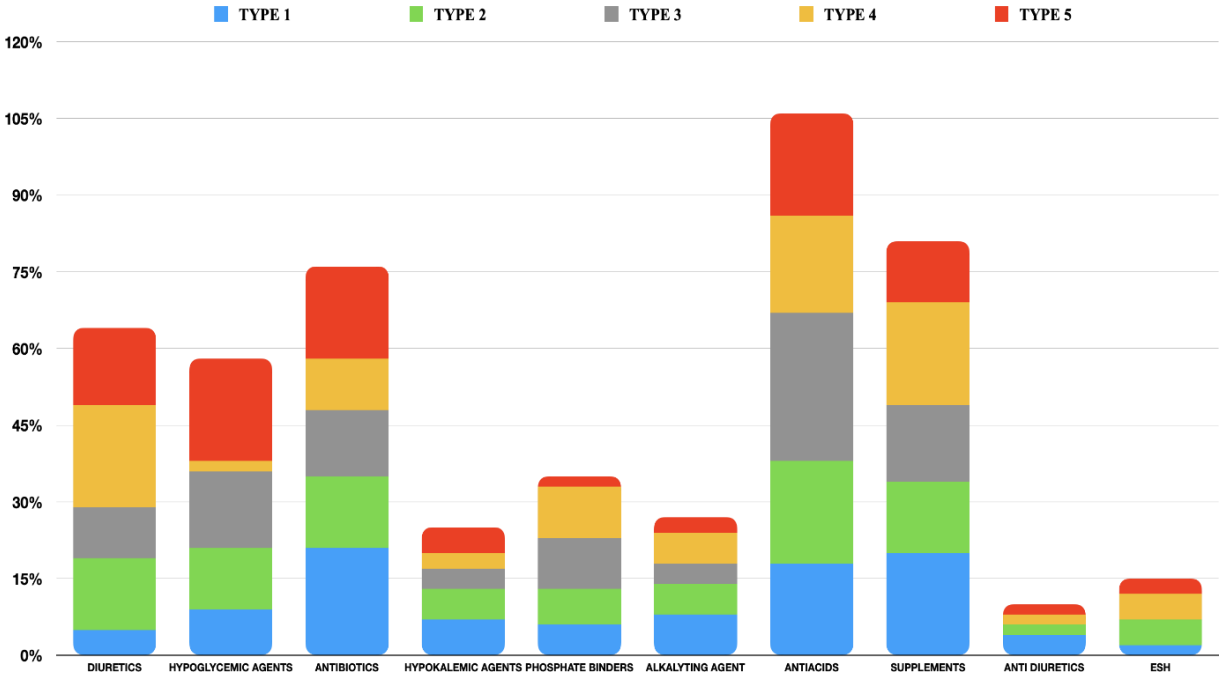


Figure 9.0 Representation of usage of renal drugs with respect to the CRS classification.

RENAL DRUGS	TYPE 1	TYPE 2	TYPE 3	TYPE 4	TYPE 5
DIURETICS	5%	14%	10%	20%	15%
HYPOGLYCEMIC AGENTS	9%	12%	13%	5%	20%
ANTIBIOTICS	21%	14%	15%	10%	18%
HYPOKALEMIC AGENTS	7%	6%	4%	3%	5%
PHOSPHATE BINDERS	6%	7%	105	105	2%
ALKALIZING AGENTS	8%	6%	4%	6%	3%
ANTIACIDS	18%	20%	29%	19%	20%
SUPPLEMENTS	20%	14%	15%	20%	12%
ANTI DIURETICS	4%	2%	0%	2%	2%
ESH	2%	5%	0%	5%	3%

STATISTICAL ANALYSIS AND MEAN STANDARD DEVIATION:

The below table shows information regarding mean, standard deviation and p-value of various variables. Here one sample analysis was performed were p values established at 95 % C-I by binomial distribution at right tail using z scores achieved through mean and standard deviation of the study data

MEAN STANDARD DEVIATION:

CHARACTERISTICS	MEAN	STANDARD DEVIATION	P-VALUES
COMORBIDITIES	1.7	0.1	0.03
THERAPY	1.6	0.4	0.03
ELECTROLYTES	1.4	0.4	0.04
AGE	69	48.7	0.05
STRUCTURAL BIOMARKERS	1.5	0.46	0.04
FUNCTIONAL BIOMARKERS	1.6	0.4	0.03
DISEASE CLASSIFICA TION	2.8	1.4	0.03
DIALYSIS	1.7	0.4	0.05
CARDIAC DRUGS	5.0	2.4	0,03
RENAL DRUGS	6.0	1.8	0.04
CHIEF COMPLAINTS	2.0	1.4	0.03
URINE OUTPUT	1.8	0.3	0.02

Table 1. Mean Standard deviation

PEARSON'S CORRELATION:

Pearson's Correlation analysis was performed by means of SPSS software between the below considered categories at C-I of 95% to achieve P values < 0.05, Co relation between given categories was done to establish the inter-dependence between the variables of the research data.

PEARSON'S CORRELATION	p VALUE
Renal drugs V/S Disease classification	0.0001
Cardiac drugs V/S Disease classification	0.0001
Chief complaints V/S Disease classification	0.0002
Comorbidities V/S Disease classification	0.0001

Table 2. Pearson's Correlation

CHI-SQUARE ANALYSIS:

Chi-Square a Nonparametric analysis was performed by means of SPSS software between the below considered categories in order to understand the association of them whether being dependent or independent or understand their patterns, her C-I was taken 95% with p-value to be less than 0.05

VARIABLES	p VALUE
Gender V/S Social history	0.00002
Gender V/S Dialysis	0.0001
Final diagnosis V/S Therapy	0.0001
Urine output V/S Type 3,4	0.0001
Disease classification V/S Functional Biomarkers	0.0001
Age V/S Social history	0.0001
Gender V/S Final diagnosis	0.0001
Dialysis V/S Type 1 & Type 2	0.00001
Disease classification V/S Structural Biomarkers	0.0001
Dialysis V/S Type 3 & Type 4	0.00001

4. DISCUSSION

This prospective observational study provides a detailed characterization of cardiorenal syndrome (CRS) in a cohort of hospitalized patients. The findings highlight several important clinical features, risk factors, and treatment patterns associated with CRS.

4.1 Prevalence of CRS Subtypes

The study demonstrated that chronic CRS subtypes (Type 2 and Type 4) were the most prevalent in our cohort. Type 2 CRS, characterized by chronic cardiac dysfunction leading to progressive CKD, accounted for 35% of cases, while Type 4 CRS, characterized by chronic kidney disease contributing to chronic cardiac abnormalities, accounted for 25% of cases. These findings are consistent with previous studies that have emphasized the significant burden of chronic comorbidities in patients with CRS [Ronco C, Di Lullo L., 2017; Epstein M, 2011]. The high prevalence of chronic CRS underscores the importance of early detection and management of underlying cardiac and renal diseases to prevent the development or progression of CRS.

In contrast, Type 3 CRS, characterized by acute worsening of kidney function causing acute cardiac dysfunction, was the least prevalent subtype, accounting for only 4% of cases. This may reflect the relatively lower incidence of primary acute kidney injury as the main driver of

CRS in this population. However, it is important to note that the incidence of each CRS type may vary depending on the specific patient population and the setting of the study.

4.2 Demographic Characteristics

The mean age of the study population was 69 years, indicating that CRS is predominantly a condition affecting older adults. This is consistent with the increased prevalence of both cardiovascular disease and chronic kidney disease with advancing age. Older adults are also more likely to have multiple comorbidities, which can further increase their risk of developing CRS.

The study also found a higher prevalence of CRS in males (67%) compared to females (33%). This gender disparity may be related to differences in the prevalence of cardiovascular risk factors, hormonal factors, or other biological and lifestyle factors. Further research is needed to fully elucidate the reasons for this gender difference.

4.3 Role of Comorbidities

Hypertension and diabetes mellitus were identified as major comorbidities in our study population. Hypertension was most prevalent in Type 4 CRS (44%), while diabetes mellitus was most prevalent in Type 4 CRS (37%). These findings are consistent with the well-established link between these traditional cardiovascular risk factors and both heart failure and chronic kidney disease [Anavekar NS, et al., 2004; Damman K, et al., 2011]. Hypertension and diabetes contribute to CRS through various mechanisms, including hemodynamic stress, inflammation, and metabolic disturbances. Effective management of hypertension and diabetes is crucial for preventing and mitigating CRS.

Coronary artery disease and heart failure were also commonly observed comorbidities, further highlighting the close relationship between cardiovascular disease and CRS.

4.4 Biomarkers in CRS

The study demonstrated the clinical utility of serum creatinine and NT-proBNP as important biomarkers in CRS. Elevated serum creatinine, a marker of renal dysfunction, was observed in 54% of Type 3 CRS patients. Elevated NT-proBNP, a marker of cardiac stress, was observed in 28% of Type 2 CRS patients. These findings support the use of these biomarkers in the diagnosis and risk stratification of CRS.

Serum creatinine is a widely used marker of renal function, and elevated levels indicate kidney injury or dysfunction. However, serum creatinine can be influenced by factors such as muscle mass and hydration status, and it may not be a sensitive marker of early kidney damage. NT-proBNP is a marker of cardiac volume overload and ventricular dysfunction. Elevated levels of NT-proBNP are associated with increased risk of heart failure and adverse cardiovascular outcomes. The combined use of serum creatinine and NT-proBNP provides a more comprehensive assessment of both cardiac and renal function in CRS.

4.5 Treatment Strategies

The study found that combination therapy, targeting both cardiac and renal dysfunction, was used more frequently (64%) than monotherapy (36%). This observation suggests that a multi-faceted approach is often necessary for the effective management of CRS.

The specific combination of therapies used varied depending on the individual patient's clinical presentation and underlying pathophysiology. However, common components of combination therapy include:

- Diuretics: To manage fluid overload.
- ACE inhibitors or ARBs: To block the renin-angiotensin-aldosterone system.
- Beta-blockers: To improve cardiac function and control heart rate.
- Mineralocorticoid receptor antagonists: To further block the effects of aldosterone.
- SGLT2 inhibitors: A newer class of medications that have shown benefits in both heart failure and CKD.

Renal replacement therapy (dialysis) was used in 24% of all CRS patients, indicating the severity of renal dysfunction in a significant proportion of these patients. The use of dialysis varied across CRS types, with the highest percentage observed in Type 5 CRS (30%).

4.6 Statistical Associations

The study revealed several statistically significant associations between clinical variables:

Comorbidities and Disease Classification: The strong correlation between comorbidities and disease classification highlights the complex interplay of underlying conditions in the development of CRS. Patients with specific comorbidities are more likely to develop certain types of CRS.

Gender and Social History: The association between gender and social history suggests potential differences in risk factors and lifestyle

behaviors between men and women with CRS.
Final Diagnosis and Therapy: The significant association between final diagnosis and therapy reflects the tailoring of treatment strategies to the specific clinical presentation and underlying cause of CRS.
Disease Classification and Biomarkers: The association between disease classification and functional and structural biomarkers underscores the utility of these biomarkers in differentiating CRS subtypes and assessing disease severity.Dialysis and Type 1 & Type 2 CRS: The association between dialysis and Type 1 and Type 2 CRS may reflect the severity of renal dysfunction in these subtypes.

4.7 Limitations

This study has several limitations that should be acknowledged:
• Single-center design: The study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other populations or healthcare settings. Multi-center studies are needed to validate these results in more diverse populations. Observational design: The observational nature of the study prevents the establishment of causality between risk factors, treatments, and outcomes. Randomized controlled trials are needed to determine the causal relationships between these variables.

• Sample size: While the sample size of 396 patients is adequate, a larger sample size could provide more statistical power to detect smaller effects and to perform more detailed subgroup analyses.In-hospital outcomes: The study focused primarily on in-hospital outcomes. Long-term follow-up data are needed to assess the impact of CRS and its management on patient survival, quality of life, and long-term renal and cardiac function.Data Completeness: Though efforts were made to ensure data completeness, there might be missing data points, which could introduce bias.

4.8 Future Directions

The findings of this study suggest several avenues for future research:
Multi-center studies: Conducting multi-center studies with larger and more diverse patient populations will enhance the generalizability of the findings.Randomized controlled trials: Performing randomized controlled trials to evaluate the efficacy and safety of different treatment strategies for CRS is essential for establishing evidence-based guidelines.

Longitudinal studies: Conducting longitudinal studies to assess long-term outcomes, including mortality, cardiovascular events, and progression of renal dysfunction, will provide a more comprehensive understanding of the impact of CRS. Novel biomarkers: Investigating novel biomarkers that can provide earlier and more accurate diagnosis of CRS, as well as predict prognosis, is a promising area of research.

Pathophysiology: Further research into the underlying pathophysiological mechanisms of CRS is needed to identify potential therapeutic targets. Artificial intelligence (AI): Exploring the potential of AI and machine learning to improve the diagnosis, risk stratification, and personalized management of CRS is an emerging field.

5. CONCLUSION:

Cardiorenal Syndrome represents a significant and escalating clinical challenge due to its complex bidirectional pathology and chronic progressive nature. This prospective study, conducted in a tertiary care setting, provides compelling evidence that chronic CRS types (II and IV) are the predominant forms encountered in hospital admissions, reflecting the long-term interplay between cardiac and renal dysfunction. Hypertension and diabetes are unequivocally identified as major drivers of CRS development and progression, underscoring the critical need for aggressive management of these underlying comorbidities.

The study reaffirms the indispensable role of readily available biomarkers such as NT-proBNP and serum creatinine as essential tools for early diagnosis, accurate assessment of disease severity, and effective prognostication in CRS patients. Their consistent elevation across various CRS types highlights their utility in routine clinical practice. Furthermore, the widespread adoption of combination therapies, targeting both cardiac and renal systems,

suggests a recognized clinical imperative for a holistic, multi-targeted approach to management, particularly in chronic CRS.

In light of the complex and multifaceted nature of CRS, an integrated care model involving a multidisciplinary team of cardiologists, nephrologists, and internists is not merely beneficial but absolutely essential for providing comprehensive assessment, tailoring individualized treatment strategies, and optimizing patient outcomes. Such collaborative care can facilitate early detection, prevent disease progression, and reduce the burden of complications.

Future research directions should prioritize several key areas to further advance our understanding and management of CRS. This includes targeted research on the identification and validation of

novel biomarkers that can offer even earlier detection and more precise risk stratification. The exploration of AI-assisted diagnostic tools holds immense promise for improving the timely recognition and accurate classification of CRS, potentially revolutionizing clinical workflows. Furthermore, large-scale, longitudinal studies with extended follow-up periods are crucial to monitor the long-term efficacy of various therapeutic strategies and their ultimate impact on patient survival, quality of life, and the prevention of adverse cardiovascular and renal events.

Finally, delving deeper into the molecular mechanisms underlying the bidirectional organ crosstalk in CRS will be vital for identifying novel therapeutic targets and developing innovative interventions to halt disease progression and ultimately enhance the quality of life for affected patients. By continuously improving our understanding and management of CRS, we can strive to reduce its significant morbidity and mortality burden.

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