A Single Centre Prospective Study of Cardiorenal Syndrome: Subtypes, Risk Factors and Outcome

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Abstract

Background and Aims: Many hospitalized patients have various degrees of heart and kidney dysfunction; which was first defined as Cardiorenal syndrome (CRS) in 2004. CRS was further divided into five subtypes depending on disease acuity and sequential organ involvements. Early recognition of this syndrome can help to reduce morbidity and mortality in these patients. Our aim of the study was to study baseline characteristics and outcomes of patients in different subtypes, and to identify various risk factors affecting outcomes. **Material and Methods:** This prospective observational study was conducted on 60 patients with CRS. Sociodemographic, laboratory, and echocardiography parameters were recorded. All patients were classified as per ACUTE DIALYSIS QUALITY INITIATIVE GROUP 2008 into various CRS sub-types. The outcome was considered favourable if patients were stable at discharge whereas, non-favourable for patients who expired or were initiated on maintenance dialysis on discharge. **Results**: Out of sixty patients (M:34, F:26, Mean age 64.23±10.83), 93.33% had comorbidity. The commonest comorbidity was DM (43, 72%) and the commonest symptom was dyspnea (60, 100%). Thirty (50%) patients had Type 1 CRS. Patients with Type 2 CRS had lower haemoglobin, calcium and mean eGFR and higher urea, creatinine, uric acid and phosphate along with higher Systolic blood pressure ($p<0.05$). The overall mortality was 10 (16.67%). Patients with higher age, lower Hb, higher creatinine, lower eGFR, low ejection fraction on admission and Type 5 CRS have non- favourable outcome (n=14, 23.33%). **Conclusion**: In conclusion, various CRS subtypes have differences in clinical features, risk factors, laboratory parameters and outcome. Patients with higher age, lower Hb, higher creatinine, lower eGFR, low ejection fraction on admission and Type 5 CRS have non- favourable outcome

Keywords: cardiorenal syndrome, CRS subtypes, risk factors, outcome

Introduction

Many hospitalized patients have various degrees of Cardiovascular and Renal systems dysfunction; in which dysfunction of one organ may induce acute or chronic dysfunction in the other organ.It is due to cardiac and renal interactions across several interfaces.It includes changes in the renin-angiotensin-aldosterone system (RAAS), the imbalance between nitric oxide (NO) and reactive oxygen species (ROS), the sympathetic nervous system activation, and inflammation.[1] The Working Group of the National Heart, Lung, and Blood Institute had first defined Cardiorenal syndrome (CRS) in 2004.[2] CRS was divided into

2 major groups, cardiorenal and renocardiac syndromes, based on the primary organ involvement.[3,4] This was further divided into five subtypes depending on disease acuity and sequential organ involvements.[5] The cardiac and renal disease together significantly increases mortality, morbidity, and cost of care.Early recognition of this syndrome can help to optimize treatment and to reduce overall disability in these patients. Studies investigating CRS profile and subtypes in India are limited.[6,7,8] Our aim of the study was to classify patients with CRS in various CRS subtypes, to study baseline characteristics and clinical outcomes of patients in different subtypes, and to identify various risk factors affecting clinical outcomes.

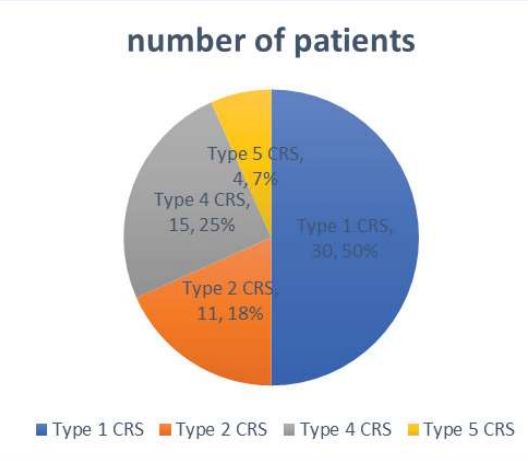
Material And Methods

This study was prospective observational study at a tertiary care hospital, Ahmedabad, Gujarat during the period between August 2018 to October 2019. Total 60 patients with CRS were taken. Patients ≥18 years were included in the study. All the patients previously diagnosed as CKD but on maintenance HD were excluded from the study. The institutional Ethics committee approval was taken and written informed consent was obtained from all the patients. In our study, NYHA functional classification was used for cardiac failure.[9] Acute kidney injury (AKI) and Chronic kidney disease (CKD) were diagnosed as per definition by KDIGO guidelines.[10] The demographic details of all patients, such as age, gender, body mass index(BMI), risk factors [hypertension, diabetes (DM), dyslipidemia, ischemic heart disease(IHD), hypothyroidism, COPD] were recorded. Various laboratory parameters, such as complete blood count (CBC), blood urea(mg/dl), s. creatinine (mg/dl) (on admission and at discharge),s. electrolytes, uric acid and estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) (on admission and at discharge) were recorded. eGFR was calculated in all patients using the MDRD study equation. Ultrasound of the whole abdomen, 24-hour urinary protein and Intact PTH (iPTH) were done to evaluate renal parenchymal disease. Electrocardiogram and 2-dimensionalechocardiography(2DECHO) were done for the cardiac function at admission. All patients were classified into various CRS subtypes according to ACUTE DIALYSIS QUALITY INITIATIVE GROUP 2008 and standard treatment was administered for the management of cardiorenal syndrome.[3] The condition was considered favourable if patients were stable at discharge whereas, non-favourable for patients who expired or were initiated on maintenance dialysis on discharge. Analysis of Data were done using SPSS. Continuous Variables were reported as mean and standard deviations. Categorical variables were reported as numbers and percentages. The Shapiro Wilk test was used to categorize the normality of data. Data were summarised using number (percentage) or median (range), as appropriate. The one-way ANOVA was used for laboratory parameters in different subgroups of CRS. Chi-square test and Unpaired t-test were used to compare thecharacteristics of patients with the favourable and non-favourable outcome. p-values <0.05 were considered statistically significant.

Results

The prevalence of CRS Subtypes is shown in Figure 1.

Figure 1. Prevalence of CRS subtypes

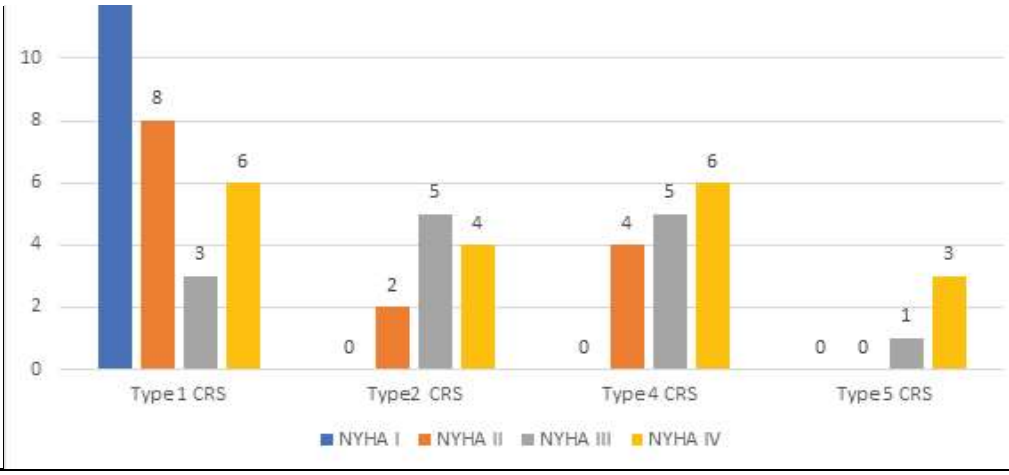


Baseline demographic and symptomatology of studied patients were described in Table 1. In this study, out of 60 patients, most (37,62%) patients belonged to the 61-80 years age group. The mean age of males was 65.09 ± 9.81 years and females were 63.31 ± 12.06 years. The mean age of patients in Type 5 CRS was higher than other subtypes though statistically not significant. (p=0.97). Among patients with Type 5 CRS, 3(75%) were female while in other subtypes there was male preponderance. In our study, all patients presented with dyspnea (n=60), most of them (19,32%) were NYHA grade 4 (Figure 2).Among our patients, pedal edema(33,55%) and pulmonary rales(33,55%) were the most common signs

Table 1.Baseline characteristics of patients in various CRS subtypes

Characteristic	CRS SUBTYPES				Total (n=60)
	Type 1 (n=30)	Type 2 (n=11)	Type 4 (n=15)	TYPE 5 (n=4)	
Mean age of patients in years	64.86 ±9.52	63.81 ± 9.45	64.33 ± 9.75	66.75 ±26.02	64.23±10.83
Male	17(56.67)	6(54.55)	10(66.67)	1(25)	34(56.66)
Female	13(43.33)	5(45.45)	5(33.33)	3(75)	26(43.33)
Dyspnea	30(100)	11(100)	15(100)	4(100)	60(100)
Chest pain	30(100)	7(63.64)	14(93.33)	1(25)	52(87)
Palpitation	24(80)	5(45.45)	11(73.33)	0	40(67)
Gabharaman	27(90)	6(54.55)	5(33.33)	2(50)	40(67)
Decrease urine output	16(53.33)	8(72.72)	7(46.67)	4(100)	35(58)
Fatigue	11(36.66)	4(36.36)	1(6.67)	4(100)	20(33)
Generalized weakness	10(33.33)	2(18.18)	1(6.67)	3(75)	16(27)
Cough with expectoration	1(3.33)	0	0	2(50)	3(5)
Pedal edema	8(26.67)	10(90.9)	11(73.33)	4(100)	33(55)
Values are presented as n (%) or as mean ± SD.					

Figure 2. NYHA classificationof patients in various CRS subtypes



In our patients, 56 (93.33%) patients had comorbidity. The commonest comorbidity was DM (43, 72%) followed by hypertension(41, 68%) (Table 2). Among studied patients, 15 patients had DM and HTN both while 11 patients had IHD along with DM and HTN both. IHD was more common in Type 1 CRS(p= 0.001) while autoimmune diseases were more common in Type 5 CRS(p=0.04).

Table 2. Risk factorsinpatients with various CRS subtypes

Risk factors	Type 1 n=30	Type 2 n=11	Type 4 n=15	Type 5 n=4	TOTAL n=60	P value
DM2	19(63.33)	11(100)	10(66.67)	3(75)	43(71.7)	0.13
Hypertension	21(70)	10(90.91)	7(46.67)	3(75)	41(68.3)	0.113
IHD	17(56.67)	11(100)	1(6.67)	0	29(48.3)	0.0001
Obesity	2(6.67)	3(27.27)	3(20)	0	8(13.3)	0.315
CKD	1(3.33)	1(9.09)	15(100)	0	16(26.7)	0.0001
Thyroid disease	1(3.33)	1(9.09)	3(20)	1(25)	6(10)	0.245
Dyslipidemia	2(6.67)	1(9.09)	3(20)	0	6(10)	0.477
COPD	1(3.33)	0	0	0	1(1.7)	0.79
Autoimmune disease	1(3.33)	0	0	1 (25)	2(3.3)	0.004
Values are presented as n (%)						

Table 3 shows laboratory and other parameters on admission in various subtypes.In our study, patients with Type 2 CRS had significantly lower haemoglobin, calcium and mean eGFRand significantly higher urea, creatinine, uric acid, potassium and phosphate ($p<0.05$).Patients with Type 2 CRS also had significantly higher Systolic blood pressure($p<0.05$). Patients with Type 4 CRS had significantly higher 24-hour urinary protein and iPTH($p<0.05$).Among these patients, abnormal USG findings were increased cortical echogenicity (15, 25%), poor CMD (7, 12%) and small kidney size (6, 10%) while 32(53%) patients had normal USG findings.

Table 3.Laboratory and other parameters on admissioninpatients with various CRS subtypes

LAB. PARA METERS	TYPE 1 n=30	TYPE 2 n=11	TYPE 4 n=15	TYPE 5 n=4	Total n=60	P value
Hb (gm/dl)	11.65±1.91	8.78±0.90	9.04±1.25	9.12±1.20	10.30 ± 2.06	<0.0001
Urea (mg/ dl)	64.89±16.68	146.27±31.37	137.94±54.00	98±48.33	100.28 ±50.06	<0.0001
Creatinine (mg/dl)	1.90±0.35	6.60±2.52	4.60±2.18	2.51±0.20	3.48 ± 2.39	<0.0001

Uric acid(mg/dl)	6.85±1.95	8.76± 0.69	6.96±2.48	6.4±2.77	7.17 ± 2.09	0.047
Sodium (mEq/L)	137.62±2.51	139.18± 7.06	135.66±5.00	140±0	137.57 ± 4.39	0.134
Potassium (mEq/L)	4.16±0.49	4.77± 0.49	5.12±0.76	3.6±0.92	4.47 ± 0.75	<0.0001
Calcium (mg/dl)	8.64±0.52	7.87±0.75	8.28±0.61	8.45±0.1	8.40 ± 0.64	0.004
Phosphate (mg/dl)	5.44±1.48	6.1±1.18	4.51±1.16	4.57±0.22	5.26 ± 1.40	0.017
24 hour urinary protein	44.50±45.11	2007.63± 898.64	2761.71± 953.54	1045±1029	1183.95 ± 1412.84	<0.0001
iPTH	37.24±26.53	137.09± 43.01	238.35±91.75	98.50±17.23	107.73± 97.11	<0.0001
Mean eGFR (ml/min/1.73 m^2)	36.06±10.30	9.45±6.05	17.56±12.55	23.65±3.99	25.73 ± 14.75	<0.0001
Number of patients with eGFR 45-60 30-44 15-29 <15	 7(23.33) 13(43.33) 10(33.33) 0	 0 0 1 (9.09) 10 (90.91)	 1 (6.67) 1 (6.67) 5 (33.33) 8 (53.33)	 0 0 4 (100) 0	 8(13.33) 14(23.33) 20(33.33) 18(30)	
Systolic Blood Pressure (SBP)	125.33±29.99	169.27± 6.64	142.42±37.70	102.00±9.09	136.00± 33.74	<0.0001
Ejection fraction(%)	33.2±7.23	31±2.72	29±9.95	28.75±11.81	31.52 ± 7.8	0.328
Number of patients with Ejection fraction 40-49% 30-39% 20-29% < 20%	 8 (26.67) 15 (50) 7 (23.33) 0	 0 9 (81.82%) 2 (18.18%) 0	 3 (20) 4 (26.67) 6 (40) 2 (13.33)	 1 (25) 1 (25) 2 (50) 0	 12(20) 29(48.33) 17(28.33) 2(3.33)	
Values are presented as n (%) or as mean ± SD.						

Table 4 shows Comparison of outcomes among various types of CRS. The overall mortality was 10 (16.67%).

Table 4. Comparison of outcomes among various types of CRS

OUTCOME	TYPE 1 (n=30)	TYPE 2 (n=11)	TYPE 4 (n=15)	TYPE 5 (n=4)	Total (n=60)	p value
STABLE	28(93.33)	8(72.73)	9 (60)	1(25)	46(76.6)	0.0043
DEATH	2 (6.67)	1(9.09)	4(26.67)	3 (75)	10(16.67)	0.0036
HD during hospitalisation	2(6.67)	5(45.45)	4(26.67)	0	11(18.33)	0.021
MAINTAINANCE HD	0	2(18.18)	2(13.33)	0	4(6.67)	0.119
MEAN DURATION OF HOSPITAL STAY	4.87 ± 2.32	5.36 ±1.80	6 ± 2.93	3.5 ±1.73	5.06 ±2.25	0.240
Values are presented as n (%) or as mean ± SD.						

Out of 60, 46 (76.67%) patients had favourable while 14 (23.33%) had non favourable outcome. Table 5 shows different variables affecting outcome.Patients with higher age, lower Hb, higher creatinine, lower eGFR and low ejection fraction on admission had a non-favourable outcome ($p<0.05$). Patients admitted with type 1 CRS had better outcome than other types. (P=0.045).

Table 5 Different variables affecting outcome in CRS

Variable	Favourable n=46	Nonfavourable n=14	p value
Age in years	62.39 ± 9.63 YEARS	70.29 ± 12.63 YEARS	0.015
Gender MALE FEMALE	 29 (63.04) 17 (36.95)	 5 (35.71) 9 (64.29)	0.070
DM2	31 (67.39)	12 (85.71)	0.183
Hypertension	31 (67.39)	10 (71.43)	0.776
IHD	26 (56.52)	3 (21.43)	0.021
CKD	10 (21.73)	6 (42.85)	0.118
Thyroid disease	3 (6.52)	3 (21.43)	0.104
Dyslipidemia	5 (10.87)	1 (7.14)	0.6840
COPD	1 (2.17)	0	0.183
Autoimmune disease	2 (4.35)	0	0.776

At Baseline			
Hb	10.58 ± 2.06	9.27 ± 1.81	0.0367
Creatinine	3.1 ± 2.09	4.71 ± 2.95	0.0261
eGFR	27.58 ± 13.73	19.02 ± 12.68	0.0422
Uric acid	7.08 ± 1.94	7.46 ± 2.6	0.556
Sodium	137.4 ± 4.06	138.14 ± 5.50	0.585
Potassium	4.4 ± 0.65	4.7 ± 1.03	0.196
Ejection fraction	33.61 ± 6.73	24.64 ± 7.26	0.0001
At discharge			
Creatinine	1.98 ± 1.58	4.63 ± 2.34	<0.0001
eGFR	41.58 ± 19.75	15.89 ± 9.91	<0.0001
Types of CRS Type 1 Type 2 Type 4 Type 5	 28 (60.87) 8 (17.39) 9 (19.57) 1 (2.17)	 2(14.29) 3(21.43) 6 (42.86) 3 (21.43)	0.045
Values are presented as n (%) or as mean ± SD.			

Discussion

The cardiorenal syndrome (CRS) term emphasized correlation between the cardiovascular and renal systems in acute or chronic disease settings.[11,12] Evolving changes in demographics have led to an aging population along with increasing rates of obesity, diabetes mellitus (DM), and hypertension. These changes can lead to concomitant occurrence of both cardiac and renal disease which was associated with a significantly increased risk of death and progression to ESRD.[13,14] In present study most of patients (30,50%) were of type 1 cardiorenal syndrome which was similar to studies conducted by HR Shah et al (46%) and Fabbian et al (48.2%).[15] In our study, mean age of patients was 64.23 ± 10.83 years while in study by HR Shah et al study and Fabbian et al mean age was 64.34 ± 15.43 and 80 ± 8 years respectively. Elderly patients often have one or more comorbidities along with the drugs for these comorbidities that may have an effect on clinical outcomes.[16,17] Therefore, elderly patients may be more susceptible to CRS.[18] In our study, mean age of patients in Type 5 CRS and Type 1 CRS was higher than other subtypes though statistically not significant. (p=0.97). In study by Antonietta et al, age was significantly different among the five CRS types ($p < 0.001$)with a higher mean age (79.9 ± 8.9 years) in patients with CRS type 1[19]. Acute heart failure in the elderly is an increasingly common clinical problem along with risk factors for AKI. Therefore, elderly patients with AHF are more susceptible to AKI (Type 1 CRS).[18] In present study, male to female ratio was (M: F -1.32:1) which was comparable to Fabbian et al(M: F -1.02:1). As mentioned in the literature, diabetes,hypertension, cardiovascular and kidney diseases are common (93.33%) in our study patients.[20] Reddy et al and H R Shah et al reported similar findings in their study. Elevated blood pressure causes cardiac and renal injury and also leads to elevated sympathetic neurohumoral activation. It also reflects an increased incidence of renal dysfunction in patients with decompensated chronic

heart failure.[21] Obesity is a central factor contributing to insulin resistance, hypertension, dyslipidemia, and chronic inflammation central to the cardio-renal-metabolic syndrome. Similarly, a strong correlation exists between obesity and proteinuria or impaired kidney function, especially with insulin resistance.[1]

In our study, patients with Type 2 CRS have significantly lower mean eGFR and higher urea and creatinine, ($p<0.05$) (Table 3). Baseline glomerular filtration rate (eGFR) is a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. Both elevated serum creatinine on admission and worsening creatinine during hospitalization also predict prolonged hospitalization, rehospitalization, and death.[22] In theVALIANTtrial[23], which included patients post MI receiving state-of-art therapy, those with eGFR below the median had 1.5 times the risk of major cardiovascular events compared with those with eGFR above the median. A meta-analysis of studies evaluating the relationship between renal dysfunction and heart failure revealed that there was a consistent risk relationship of a 7% increase in mortality for every 10 mL/min decrease in eGFR.[24,25] A meta-analysis by Tonelli et al.[26] conducted on 1.4 million patients found higher mortality rates for all causes with eGFR decline with relative death odds ratios of 1.9, 2.6 and 4.4 for GFR levels of 80, 60 and 40 ml/min, respectively.

Patients with Type 2 CRS in our study also have significantly lower Hb. Anaemia is present in CKD and CHF patients and also among patients with preserved and depressed LVEF[27]. Anemia is considered to be one of the most important factors along wi th hypertension for the development of LVH in CKD patients which can leads to worse outcomes.[7,1]

In present study, patients with Type 2 and Type 4 CRS have significantly higher iPTH ($p<0.00010$ while patients with Type 2 CRS have significantly higher phosphate level($p=0.017$). Hyperphosphatemia, observed in CKD, is associated with cardiac hypertrophy, which may worsen cardiac contractility and heart failure. Studies have also shown an association of high-normal serum phosphate levels and secondary hyperparathyroidism (also described as CKD mineral and bone disorder) with vascular and valvular calcificationand progression of heart failure.[28]Patients with Type 4 CRS have significantly higher 24-hour urinary protein($p<0.05$). Proteinuria has been associated with increased cardiovascular mortality.In repeated studies, the presence of mi cro-and macroalbuminuria and GFR reduction were independent predictors of increased overall andcardiovascular mortality in both diabetic patients and non-diabetic patients[29,30].

Patients with Type 2 CRS and Type 4 CRS also have significantly higher Systolic blood pressure($p<0.05$). Tight blood pressure control in patients with CKD isassociated with reduced CV risk and a reduced rate of declinein renal function[31].In our study, patients with Type 5 CRS have lower EF compared to other subtypes thoughstatistically not significant.In study by Mavrakanas[32] et al, along with the baseline clinical characteristics, three echocardiographic parameters, LVEF, pulmonary artery pressure, and RV diameter were independently associated with the occurrence of cardiorenal syndrome. Metra et al.[33] have reported that LVEF is an independent predictor of worsening kidney function among patients with acute HF. On the contrary, in the ESCAPE Trial, hemodynamic parameters, includingwedge pressure and cardiac index, in patients with pulmonary artery catheter–guided therapy were not independent predictors of worsening kidney function[33].

The overall mortality in our patients is 16.7%.The overall mortality in study by H R Shah et al, Reddy et al and Antonietta et al is 16%, 6.32% and13.6% respectively.Mortality was higher in patients admitted with Type 5 CRS (75%)($p=0.003$) in our study.In study by H R Shah et al, Reddy et al and Antonietta et al;mortality was higher in CRS 5, CRS 4 and CRS 1 respectively. In our study, patients with Type 5 CRS have higher mean age,predominant(75%) female gender, mostly(75%) presented with NYHA grade 4 dyspnoea, all having associated comorbidity and all having mean eGFR <30 **(**ml/min/1.73 m^2**)**which can be the reason of high mortality in this subgroup.

In our study, patients with higher age, lower Hb, higher creatinine, lower eGFR and low ejection fraction on admission and Type 5 CRS had a non-favourable outcome which was statistically significant ($p<0.05$).In present study, co-morbidities had no impact on outcome of patients. In study by Reddy et al, BUN ($P < 0.001$), creatinine ($P < 0.001$), potassium ($P < 0.001$), albumin ($P < 0.001$), and eGFR ($P < 0.001$) were associated with the outcomes in patients with CRS. In study by H R Shah et al, higher

age, higher creatinine, low eGFR and low ejection fraction associated with non-favourable outcome. Our study has certain limitations.First, our sample size issmall.Second, we do not consider patient's transit from one sub type to another during hospital stay. Third, we do not have follow up of patients after discharge.

Conclusion

Cardiorenal syndrome shows inescapable link between cardiovascular system and renal system. Various CRS subtypes have many common pathophysiological mechanisms but still have differences in clinical features, risk factors, laboratory parameters and clinical outcome. Higher age, lower Hb, higher creatinine, lower eGFR and low ejection fraction on admission are factors affecting outcome adversely. Type 5 CRS patients have worst clinical outcome in our study. As our study has small sample size future studies are required to validate the results.

References

1. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, *et al*. Cardiorenal syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: A scientific statement from the American Heart Association. Circulation 2019;139:e840-78.
2. National Heart, Lung, and Blood Institute. NHLBI Working Group: cardiorenal connections in heart failure and cardiovascular disease, 2004. https://www.nhlbi.nih.gov/events/2004/cardio-renal-connections-heartfailure-and-cardiovascular-disease. Accessed February 15, 2018.
3. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the Consensus Conference of the Acute Dialysis Quality Initiative. *Eur Heart J*. 2010; 31:703–711.
4. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008; 52:1527–1539. doi: 10.1016/j. jacc.2008.07.051
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004; 8:R204–R212.
6. Bhattacharya PK, Roy A, Jamil M, Barman B, Murti SV, Marak PR. Clinical profile and determinants of short-term outcome of acute kidney injury: A hospital-based prospective study from Northeastern India. J Lab Physicians 2019;11:5-10.
7. Shah HR, Singh NP, Aggarwal NP, Singhania D, Jha LK, Kumar A. Cardiorenal syndrome: Clinical outcome study. J Assoc Physicians India. 2016 Dec 1;64(12):41.
8. Reddy MP, Madappa NU, Hegde A, Prakash V S. A prospective single center study to assess the incidence and risk factors associated with cardiorenal syndrome with respect to its subtypes. J Pract Cardiovasc Sci 2020;6:162-8
9. Lainscak M, Spoletini I, Coats A. Definition and classification of heart failure. Int Cardiovasc Forum J 2017;10:3-7.
10. Singh K, Waikar SS, Samal L. Evaluating the feasibility of the KDIGO CKD referral recommendations. BMC Nephrol 2017;18:223.
11. Clementi A, Virzì GM, Brocca A, de Cal M, Vescovo G, Granata A, Ronco C. Cardiorenal syndrome type 4: management. Blood Purif. 2013;36(3-4):200-9.
12. Suresh H, Arun BS, Moger V, Swamy M. Cardiorenal syndrome type 4. A study of cardiovascular diseases in chronic kidney disease. Indian Heart J 2017;69:11-6.
13. Cruz DN, Bagshaw SM. Heart-kidney interaction: epidemiology of cardiorenal syndromes. Int J

Nephrol. 2010;2011:351291.
14. Matsushita K, van der Velde M, Astor BC, et al: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 375:2073–2081, 2010.
15. Fabbian F, Pala M, De Giorgi A, Scalone A, Molino C, Portaluppi F, Mikhailidis DP, Manfredini R. Clinical features of cardio-renal syndrome in a cohort of consecutive patients admitted to an internal medicine ward. The open cardiovascular medicine journal. 2011;5:220
16. Oudejans I, Mosterd A, Bloemen JA, Valk MJ, van Velzen E, Wielders JP, Zuithoff NP, Rutten FH, Hoes AW: Clinical evaluation of geriatric outpatients with suspected heart failure: Value of symptoms, signs, and additional tests. Eur J Heart Fail 2011;13:518-527.
17. Wehling M: Morbus diureticus in the elderly: Epidemic overuse of a widely applied group of drugs. J Am Med Dir Assoc 2013;14:437-442.
18. Hu W, He W, Liu W, Fang X, Wu Y, Yu F, Hao W. Risk factors and prognosis of cardiorenal syndrome type 1 in elderly Chinese patients: a retrospective observational cohort study. Kidney and Blood Pressure Research. 2016;41(5):672-9.
19. Gigante A, Liberatori M, Gasperini ML, Sardo L, Di Mario F, Dorelli B, *et al*. Prevalence and clinical features of patients with the cardiorenal syndrome admitted to an internal medicine ward. Cardiorenal Med 2014;4:88-94.
20. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, *et al*. Heart failure in chronic kidney disease: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:1304-17.
21. Banerjee S, Panas R. Diabetes and cardiorenal syndrome: Understanding the "Triple Threat." Hellenic J Cardiol2017;58:342-7.
22. Gottlieb SS, Abraham WT, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002; 8:136 –141.
23. Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906.
24. Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: Systematic review and meta-analysis. J Am Coll Cardiol2006;47:1987-96.
25. PP Liu. Cardiorenal syndrome in heart failure: A cardiologist's perspective. Can J Cardiol 2008;24(Suppl B):25B-29B
26. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17: 2034–2047.
27. Cruz DN, Schmidt-Ott KM, Vescovo G, House AA, Kellum JA, Ronco C, McCullough PA, Acute Dialysis Quality Initiative. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). In ADQI Consensus on AKI Biomarkers and Cardiorenal Syndromes 2013 (Vol. 182, pp. 117-136). Karger Publishers.
28. Christopoulou EC, Filippatos TD, Megapanou E, Elisaf MS, Liamis G. Phosphate imbalance in patients with heart failure. Heart failure reviews. 2017 May 1;22(3):349-56.
29. Ninomiya T, Perkovic V, De Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. JASN. 2009;20(8):1813–1821.
30. Astor BC, Hallan SI, Miller ER, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. Am J Epidemiol. 2008;167(10):1226–1234.
31. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, O'Connor A, Perumal K, Rahman M, Steigerwalt S, Teal V, Townsend R, Weir M, Wright JT Jr: Hypertension awareness, treatment, and control in adults with CKD: results from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis 2010; 55: 441–451.

32. MavrakanasTA, Khattak A, Singh K, Charytan DM. Epidemiology and natural history of the cardiorenal syndromes in a cohort with echocardiography. Clin J Am Soc Nephrol. 2017;12:1624–33.

33. MetraM, Nodari S, Parrinello G, Bordonali T, Bugatti S,Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei Cas L: Worsening renal function in patients hospitalised for acute heart failure: Clinical implications and prognostic significance. Eur J Heart Fail 10: 188–195, 2008 22.

34. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA: Cardiorenal interactions: Insights from the ESCAPE trial. J Am Coll Cardiol 51: 1268–1274, 2008