ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Clinical Profile, Etiology, Classification And Outcome Of Cardio-Renal Syndrome At Tertiary Care Teaching Hospital In Western Maharashtra, India.

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ABSTRACT

The cardiorenal syndrome (CRS) is a complex disease in which heart and kidney are simultaneously affected resulting in accelerated progression of renal and myocardial damage. This study was conducted at tertiary care teaching hospital in western Maharashtra. This was a prospective observational study which was conducted over one year duration in patients with diagnosis of CRS admitting in medical intensive care unit and medical wards. Total 110 (50.6 ±9.34 years) patients fulfilling criteria of cardio-renal syndrome were included in this study. Total 51.81% patients had type 1 CRS, 2.72% type 2, 10% type 3, 2.72% type 4 and 27.27% had type 5 CRS. Type 1 CRS was most common and next was type 5 CRS ('p' <0.002). Total 15.45% patients presented with pulmonary edema, 22.72% with hypertension, 27.27% had type-2 diabetes mellitus, 8.18% with AKI, 10.90% with septicemia, 13.63% with acute coronary syndrome (ACS). Total 50% patients had diastolic dysfunction. Significant proportion (more than one third) of population had hypertension, diabetes mellitus and or IHD as pre-existing co-morbidity in patient with diagnosis of CRS ('p' <0.03). Total 79.09% patients with CRS received pharmacotherapy and 20.90% received ultrafiltration as a treatment modality. Overall case fatality rate for CRS was 8.18%. The present study highlighted majority of patient had type 1 and 5 cardiorenal syndrome. The significant number of patients with cardio-renal syndrome had diastolic dysfunction with preserved left ventricular ejection fraction. Hypertensive heart disease and IHD and diastolic dysfunction with preserved LVF were the most common associated findings for type 1 cardiorenal syndrome. The use of CRS classification can help physicians to characterize groups of patients, provides the risk stratification, rationale and specific management for better outcome of CRS.

Keywords: Cardiorenal syndrome, hypertension, diastolic dysfunction, pulmonary edema, ultrafiltration.

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ISSN: 0975-8585

INTRODUCTION

The cardiorenal syndrome (CRS) is a complex disease in which heart and kidney are simultaneously affected with accelerated progression of renal and myocardial damage. Cardiorenal dysfunction is usually secondary to multiple factors acting in concert.[1] The term cardiorenal syndrome (CRS) has been variably defined in the last decades.[2] Cardiorenal syndromes (CRS) is a disorder of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other, accordingly five different types of cardio-renal syndrome are described.[3] CRS is a state in which advanced congestive heart failure (CHF) becomes complicated by acute impairment of kidney function. The primary changes in cardiac function in which therapy to relieve CHF symptoms is limited by further worsening renal function.[2] Decreased renal function predicts cardiovascular mortality and complicates heart failure. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. Patients with chronic renal insufficiency are at strikingly higher risk for myocardial infarction, HF with systolic dysfunction, HF with preserved left ventricular ejection fraction and death resulting from cardiac causes compared with individuals with normal GFR. CRS has garnered much attention from both the cardiological and nephrological and intesivists communities due to associated significant morbidity and mortality. Cardiorenal syndrome (CRS) is the umbrella term used to describe clinical conditions in which cardiac and renal dysfunctions coexist.[4] So far there is scarcity of data regarding clinical profile and outcome of this cardiorenal syndrome, this study was conducted to elucidate the same.

MATERIAL AND METHODS

This study was conducted at tertiary care teaching hospital in western Maharashtra. This was a prospective observational non-interventional study which was conducted over one year duration from January 2014 to December 2014 in patients with CRS admitting in medical intensive care unit and medical wards. The patients with diagnosis of Cardio-renal syndrome of both genders with age ≥ 18 years were included in this study. Detailed physical examination was done. The detailed history about risk factors, co-morbidities (CKD, HTN, CAD, DM) and drug intake were taken. Blood investigations were done for hemoglobin, blood sugar level, blood urea, serum creatinine, serum electrolytes (Na+, K^+, Ca^{++}, Po_4^{++}), arterial blood gas analysis, lipid profile, serum uric acid, . Urine analysis for microsopy, proteinuria and if required culture sensitivity was done. GFR was calculated by standard formula. Chest radiogram, Electrocardiogram (ECG) (for ischemic changes, STEMI, non-STEMI, Hyperkalemia, Hypokalemia, LV hypertrophy), two-dimensional transthorasic echocardiogram (LV wall IVS thickness, systolic function, diastolic function, regional wall motion abnormalities, pulmonary artery pressure) ultrasound abdomen (kidney size and medical renal disease) of all patients was taken.[5] Aims & objectives: To study the demographic, clinical presentation, etiological, laboratory and imaging profile of cardio-renal syndrome (CRS) and to study outcome of CRS**.**

Definition and classification of the Cardio-Renal Syndromes [6]

Cardio-Renal Syndromes (CRS) general definition

1. Acute Cardio-Renal Syndrome (Type 1): Acute worsening of cardiac function leading to renal dysfunction
2. Chronic Cardio-Renal Syndrome (Type 2): Chronic abnormalities in cardiac function leading to renal dysfunction
3. Acute Reno-Cardiac Syndrome (Type 3): Acute worsening of renal function causing cardiac dysfunction
4. Chronic Reno-Cardiac Syndrome (Type 4): Chronic abnormalities in renal function leading to cardiac disease;
5. Secondary Cardio-Renal Syndromes (Type 5): Systemic conditions causing simultaneous dysfunction of the heart and kidney

Inclusion criteria: All patients had worsened renal function (defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter) within 12 weeks before or 10 days after the index admission for heart failure. Patients with a serum creatinine level of more than 3.5 mg per deciliter at the time of admission. All patients were required to have at least two of the following conditions: at least 2+ peripheral edema, jugular

venous pressure greater than 10 cm of water, or pulmonary edema or pleural effusion on chest radiography supported by echocardiographic findings.[7]

1. Fluid status was managed by means of ultrafiltration. Ultrafiltration was performed at a fluid-removal rate of 200 ml per hour. The addition of intravenous vasodilators or positive inotropic agents.
2. For patients assigned to intensive stepped pharmacologic therapy, intravenous diuretics were used to manage signs and symptoms of congestion.
3. Diuretics doses were adjusted to maintain a desired urine output and to relive features of heart failure
4. The use of intravenous vasodilators and inotropic agents for patients in whom the target urine output could not be attained were based on the individual patient's blood pressure, ejection fraction, and the presence or absence of right ventricular failure[7]

All patients were treated with intensive stepped pharmacologic therapy and or ultrafiltration the signs and symptoms of congestion in the patient were reduced to the best extent possible (discharge or death). Diuresis or ultrafiltration were slowed or temporarily discontinued according to clinical care requirements, as determined by the clinical assesment.[7] The rate of clinical decongestion and measures of global well-being and dyspnea. Clinical decongestion was defined as jugular venous pressure of less than 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea.[7] Chronic Kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) <60.0ml/min/ 1.73m2 for three months or more irrespective of the cause. [eGFR (mL/min/1.73 m2) = 186 × (Sr. Cr)–1.154 × (Age)–0.203 × (0.742, if female)]. Stages of CKD: Stage 1: normal eGFR ≥ 90 mL/min per 1.73 m^2 and persistent albuminuria. Stage 2: eGFR between 60 to 89 mL/min per 1.73 m^2. Stage 3: eGFR between 30 to 59 mL/min per 1.73 m^2. Stage 4: eGFR between 15 to 29 mL/min per 1.73 m^2. Stage 5: eGFR of < 15 mL/min per 1.73 m^2 or end-stage renal disease. Statistical analysis: Clinical data, Laboratory findings and type of CRS was recorded in data entry sheet and analysed by statistical software package (SPSS) version, 11. The mean, standard deviation percentage and chi-square test. The 'p' value < 0.05 was considered as statistically significant.

RESULTS

Total 110 patients fulfilling criteria of cardio-renal syndrome were included in this study. Of total 110 (50.6 ±9.34 years) patient with cardio-renal syndrome 69 (62.72%) were males and 41 (37.27%) were females with mean age of 53.67 (±9.75) and 47.53 (±8.93) respectively. [Table no.1] Total 57 (51.81%) patients with type 1 Cardio-renal syndrome (CRS) [Acute Cardio-Renal Syndrome: an acute worsening of cardiac function leading to renal dysfunction], 33 (57.89%) were males and 24 (42.10%) were females. Total 3 (2.72%) patients with type 2 CRS [Chronic Cardio-Renal Syndrome: chronic abnormalities in cardiac function leading to renal dysfunction], 2 (66.66%) were males and 1(33.33%) were females. Total 9 (10%) patients with type 3 CRS [Acute Reno-Cardiac Syndrome: an acute worsening of renal function causing cardiac dysfunction], 6 (66.66%) were males and 3(33.33%) were females. Total 11(2.72%) patients with type 4 CRS [Chronic Reno-Cardiac Syndrome: chronic abnormalities in renal function leading to cardiac disease], 7 (63.63%) were males and 4(36.36%) were females. Total 30 (27.27%) patients with type 5 CRS [Secondary Cardio-Renal Syndromes: systemic conditions causing simultaneous dysfunction of the heart and kidney], 21 (70%) were males and 9(30%) were females. Type 1 CRS was most common and next was type 5 CRS ('p' <0.002). [Table no.2] [Figure no. 1 & 2] Mean and standard deviation of numerical variables of laboratory and echocardiographic variables are given in table number 3. Of total 15 (13.63%) patients, 9 (13.04%) were males and 6 (14.63%) were females, presented with coronary artery disease (CAD). Of total 17 (15.45%) patients, 11 (15.94%) were males and 6 (14.63%) were females, presented with pulmonary edema. [Figure no.4] Of total 25 (22.72%) patients, 15 (21.73%) were males and 10 (24.39%) were females, presented with hypertension. [Figure no. 2] Of total 3 (2.72%) patients, 2 (2.89%) were males and 1 (2.43%) were females, presented with dilated cardiomyopathy. [Figure no. 3] Of total 9(8.18%) patients, 6 (6.69%) were males and 3 (7.31%) were females, presented with acute kidney injury. Of total 11(10%) patients, 7(10.14%) were males and 4 (9.75%) were females, presented with chronic kidney injury. Of total 12(10.90%) patients, 8(11.59%) were males and 4 (9.75%) were females, presented with septicemia. Of total 9(8.18%) patients, 3(4.34%) were males and 6 (14.63%) were females, presented with urinary tract infection. Of total 7(6.36%) patients, 5 (7.24%) were males and 2 (4.87%) were females, presented with pneumonia. Of total 2(1.81%) patients, 2 (2.89%) were males, presented with decompensated Liver cirrhosis with additionally hepato-renal syndrome. [Table no. 4] Total 15 (13.63%) patients had acute coronary syndrome (ACS) at the time of presentation [Males: 9 (13.04%) and Females: 6

(14.63%)]. Total 13 (11.81%) patients had left ventricular hypertrophy (LVH) on echocardiogram [Males: 8(11.59%) and Females: 5 (12.19%)]. Total 3 (2.72%) patients had Dilated cardiomyopathy on echocardiogram [Males: 2(2.89%) and Females: 1 (2.43%)]. Total 3 (2.72%) patients had LVEF (<30%) [Males: 2(2.89%); Female 1 (2.43%). [Figure no. 3] Total 72 (65.45%) patients had LVEF > 50% [55 (79.71%); 17 (34.59%)]. Total 35 (33.81%) patients had LVEF (≥30% - ≤50% [Males:12 (17.39%); Females: 23 (56.09%)]. Total 55 (50%) patients had diastolic dysfunction [Males: 33 (47.82%); Females: 22(53.65%)]. [Figure no. 3] Total 11 (10%) patient had chronic kidney disease (CKD) [Males: 7(10.14%); Females:4(9.75%)]. Total 21 (19.09%) patients had medical renal disease (MRD) [Males: 14(20.28%); Females: 7(17.07%)]. Total 13 (11.81%) patients had multi-organ dysfunction (MOD) [Males: 8 (11.59%); Females:5 (9.31%)]. Total 37 (33.63%) metabolic-encephalopathy (Males:25(36.23%); Females: 12(29.26%)]. Total 100 (90.90%) patient had metabolic acidosis on arterial blood gad analysis (ABGA) [Males: 62(89.85%); Females 38 (92.68%)]. Total 27 (24.54%) patient had oliguria at the time of admission [Males: 17(24.63%); Females: 10(24.39%)]. Total two (1.81%) patient had cardiogenic shock [Males: 2(2.89%)]. Total 35 (53.84%) patients had hypotension [Males: 23 (52.27%); Females: 12(57.14%)]. Total 9(8.17%) patients had hyperkalemia [Males: 6(9.1%); Females: 3(7.28%)]. Total 7 (6.5%) patients had hypokalemia [Males:5(8.3%); Females:2 (5.3%)]. [Table no. 5] Total 15 (27.27%) patients had type-2 diabetes mellitus [Males: 9 (25.71%) and Females: 6 (30%)]. Total 18 (32.72%) patients had hypertension (HTN) [Males: 11(31.42%) Females:7(35%)]. Total 12 (21.81%) patients had ischemic heart disease (IHD) [Males: 9 (25.71%) Females:3 (15%)]. Total 5 (9.09%) patients had chronic obstructive pulmonary disease (COPD) [Males: 3 (8.57%) Females:2(10%)]. Total 5 (9.09%) patients had Stroke [Males: 3 (8.57%); Females: 2(10%)]. Significant proportion (more than one third) of population had hypertension, diabetes mellitus and or IHD as pre-existing co-morbidity in patient with diagnosis of CRS ('p' <0.03). [Table no. 6] [Figure no. 2] Total 87 (79.09%) patients with CRS received pharmacotherapy (diuretic-based stepped pharmacologic therapy) as a treatment modality [males: 45 (65.21%) and females: 23 (56.09%)]. Total 23 (20.90%) patients with CRS received ultrafiltration/ hemodialysis as a treatment modality [males: 24 (34.78%) and females: 18 (43.9%)]. Majority of patients with CRS received pharmacotherapy as a treatment modality ('p' <0.01). [Table no. 7] [Figure no. 2] Of total 110 patients with CRS, 62 (89.85%) males and 39 (95.12%) females were discharged after achieving desirable clinical and laboratory parameters. Total 9 patients with CRS, 7 (10.14%) males and 2 (4.87%) females were succumbed during treatment.[Table no. 8] The mortality rate was high amongst patients with CKD (type 4) and type 5 cardio-renal syndrome ('p' <0.023). Relatively the mortality rate was more in male 10.14% than female (4.87%) population. Overall case fatality rate for CRS was 8.18%. Type 1, 2, and 3 CRS had relatively less mortality ('p' <0.05).

Table 1: Demographic profile of patients with Cardiorenal syndrome

Variable	n=110	%	Mean age (years)	±SD
Males	69	62.72	53.67	±9.75
Females	41	37.27	47.53	±8.93
Total	110	100	50.6	±9.34

Table 2: Demographic distribution of patients with type of Cardiorenal syndrome

Type of CRS	Total n=110	%	Males n=69	%	Females n=41	%
Type-1	57	51.81	33	57.89	24	42.10
Type-2	3	2.72	2	66.66	1	33.33
Type-3	9	8.18	6	66.66	3	33.33
Type-4	11	10	7	63.63	4	36.36
Type-5	30	27.27	21	70	9	30
Total	110	100	69	62.72	41	37.27

ISSN: 0975-8585

Table 3: Laboratory and echocardiographic profile of patients with Cardiorenal syndrome

Variables	mean	SD	mean	SD	Mean	SD
	Total (n=110)		Males (n=69)		Females (n=41)	
Creatinine	7.9	4.1	8.5	3.7	7.2	3.5
BUL	117	56	129	67	106	55
Potassium	7.2	2.1	6.9	2.4	7.1	3.7
Sodium	146	11	147	12	139	7
ABGA	7.1	0.2	7.2	0.11	7.11	0.23
LVEF	55.54	9.08	56.33	8.73	54.36	7.33
LVPW	1.23	0.44	1.34	0.22	1.41	0.25
E/A ratio	0.76	0.13	0.67	0.23	0.63	0.22
SBP	160	40	166	44	152	36
DBP	96	32	98	30	92	34
eGFR	66	22	64	24	58	18

Table 4: Clinical presentations of patients with Cardiorenal syndrome

Clinical variables	Total (n=110)	%	Males (n=69)	%	Females (n=41)	%
CAD (Type-1 CRS)	15	13.63	9	13.04	6	14.63
Pulmonary edema (Type-1)	17	15.45	11	15.94	6	14.63
Hypertension (Type-1)	25	22.72	15	21.73	10	24.39
Cardiomyopathy (Type-2)	3	2.72	2	2.89	1	2.43
AKD ± AGE (Type-3)	9	8.18	6	8.69	3	7.31
CKD ± cellutitis (Type-4)	11	10	7	10.14	4	9.75
Septicemia ± cellulitis (Type-5)	12	10.90	8	11.59	4	9.75
UTI (Type-5)	9	8.18	3	4.34	6	14.63
Pneumonia (Type-5)	7	6.36	5	7.24	2	4.87
Liver Cirrhosis (Type-5)	2	1.81	2	2.89	0	0
Total	110	100	69	100	41	100

Table 5: Diagnosis, clinical and laboratory interpretation of patients with Cardiorenal syndrome

Clinical variables	Total N=110	%	males n=69	%	females n=41	%
Acute coronary syndrome	15	13.63	9	13.04	6	14.63
Left ventricular hypertrophy	13	11.81	8	11.59	5	12.19
Dilated cardiomyopathy	3	2.72	2	2.89	1	2.43
LVEF (<30%)	3	2.72	2	2.89	1	2.43
LVEF (> 50%)	72	65.45	55	79.71	17	34.59
LVEF (≥30% - ≤50%)	35	33.81	12	17.39	23	56.09
Diastolic dysfunction	55	50	65	94.20	22	53.65
CKD	11	10	7	10.14	4	9.75
Medical renal disease (MRD)	21	19.09	14	20.28	7	17.07
MOD	13	11.81	8	11.59	5	9.317
Metabolic-encephalopathy	37	33.63	25	36.23	12	29.26
Metabolic acidosis	100	90.90	62	89.85	38	92.68

ISSN: 0975-8585

Oliguria, (U/O <400 mL/24 h)	27	24.54	17	24.63	10	24.39
Cardiogenic shock	2	1.81	2	2.89	0	0
Hypotension	35	53.84	23	52.27	12	57.14
Hyperkalemia	9	8.17	6	9.1	3	7.28
Hypokalemia	7	6.5	5	8.3	2	5.3

Table 6: Pre-existing Co-morbidities of patients with Cardiorenal syndrome

Co-morbidities	Total N=110	%	males n=69	%	females n=49	%
Diabetes mellitus	15	27.27	9	25.71	6	30
Hypertension	18	32.72	11	31.42	7	35
IHD	12	21.81	9	25.71	3	15
COPD	5	9.09	3	8.57	2	10
Stroke	5	9.09	3	8.57	2	10
Total	55	100	35	100	20	100

Table 7: Treatment modalities used to treat patients with Cardiorenal syndrome

Treatment modality of CRS	Total N=110	%	males n=69	%	Females n=41	%
Pharmacotherapy	87	79.09	45	65.21	23	56.09
Ultrafiltration	23	20.90	24	34.78	18	43.90
Total	110	100	69	100	41	100

Table 8: Clinical outcome of patients with Cardiorenal syndrome

Variables of Outcome	Males n=69	%	females n=41	%	Total N=110	%
Discharged	62	89.85	39	95.12	101	91.81
Death	7	10.14	2	4.87	9	8.18
Total	69	100	41	100	110	100

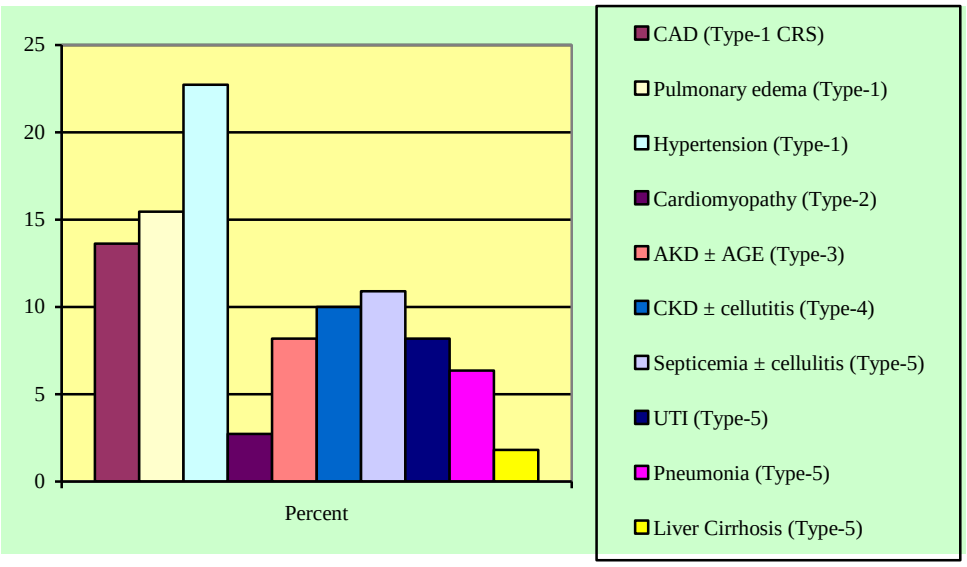

Figure 1: Etiological classification of various types of Cardiorenal syndrome

ISSN: 0975-8585

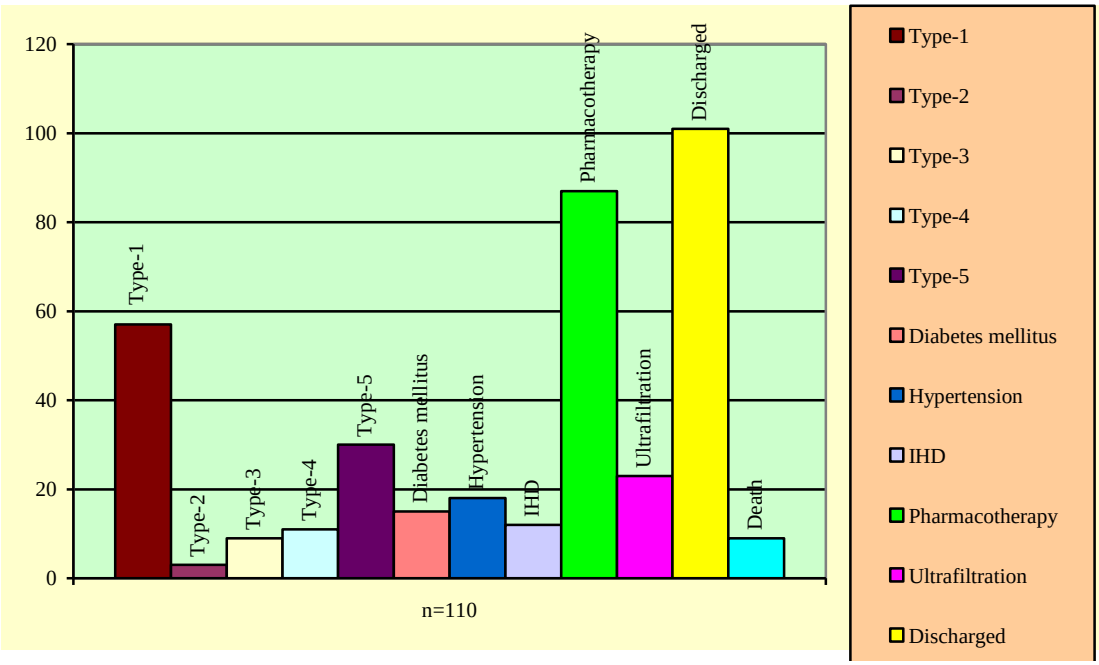

Figure 2: Classification, co-morbidities, treatment modality and outcome of Cardiorenal syndrome

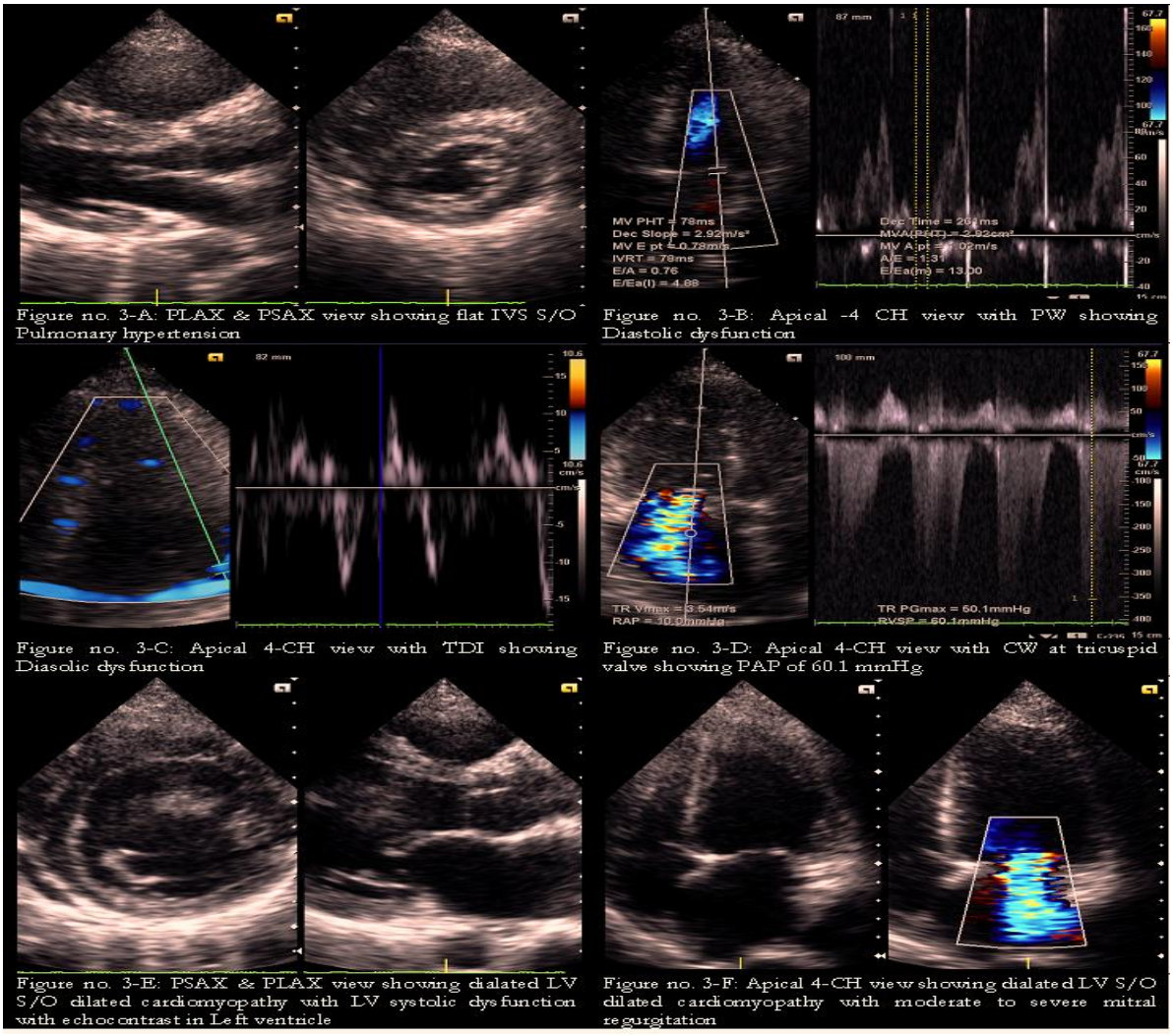

Figure 3: Echocardiographic profile of patients with various cardiorenal syndrome

ISSN: 0975-8585

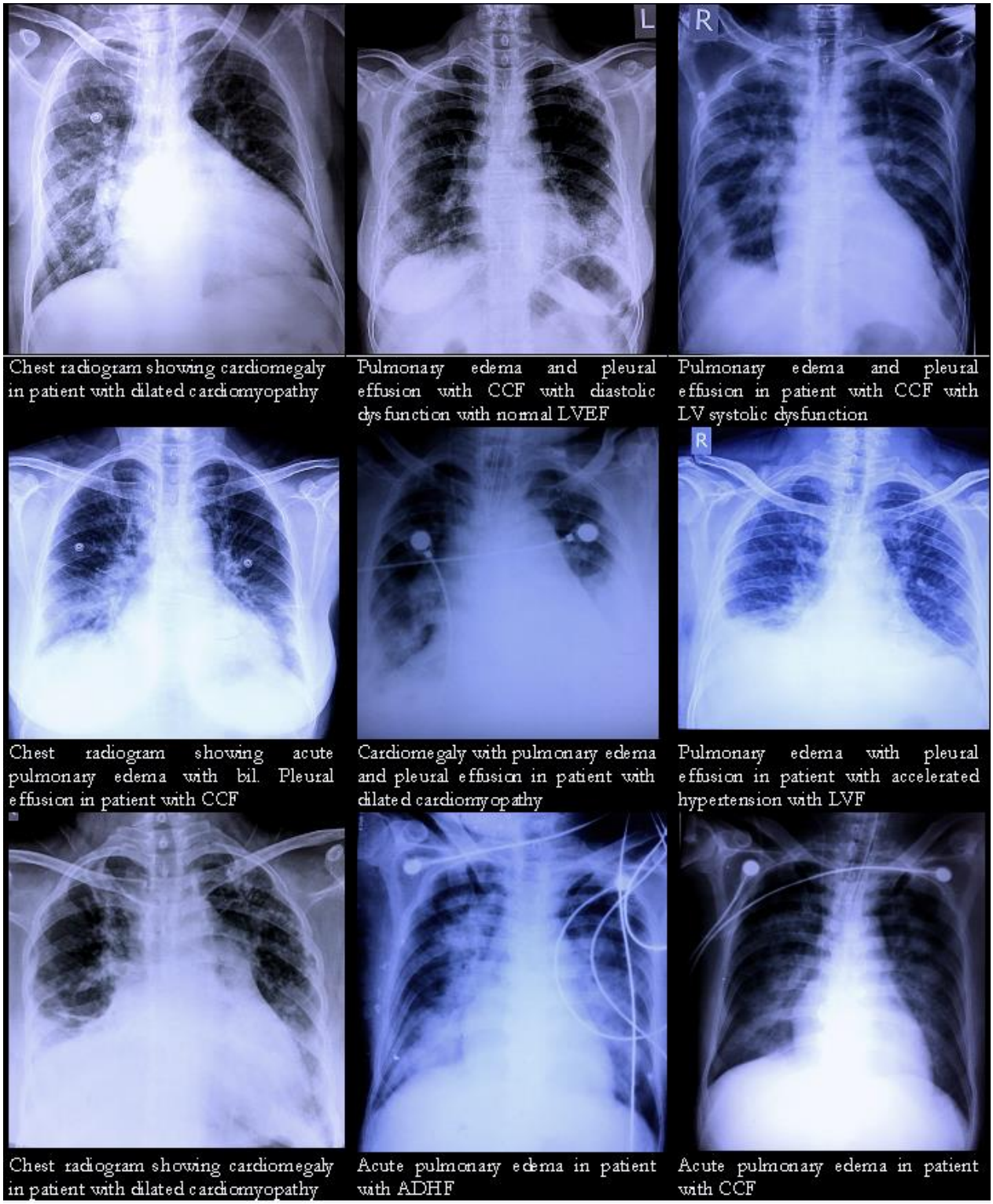

Figure 4: Chest radiogram showing different presentations of various cardiorenal syndrome

DISCUSSION

The cardiorenal syndrome (CRS) is a complex disease in which heart and kidney are simultaneously affected and their deleterious effects are reinforced in a feedback cycle, with accelerated progression of renal and myocardial damage. CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other. Type 1 CRS reflects an abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated

congestive heart failure) leading to acute kidney injury. Type 2 CRS comprises chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive chronic kidney disease. Type 3 CRS consists of an abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction (e.g. heart failure, arrhythmia, ischemia). Type 4 CRS describes a state of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects a systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction. Biomarkers can contribute to an early diagnosis of CRS and to a timely therapeutic intervention.[8] Cardiorenal syndrome (CRS) is the umbrella term used to describe clinical conditions in which cardiac and renal dysfunctions coexist. Much has been written on this subject, but underlying pathophysiological mechanisms continue to be unravelled and implications for management continue to be debated.[4] A classification system incorporating five subtypes has recently been proposed though it has yet to permeate into day-to-day clinical practice. Renal dysfunction is highly prevalent amongst patients with heart failure and has been shown to be as powerful and independent a marker of adverse prognosis as ejection fraction. Similarly, patients with renal failure are considerably more likely to suffer cardiovascular disease than matched subjects from the general population. The cardio-renal syndromes (CRS) recently were defined systematically as disorders of the heart or kidney whereby dysfunction of one organ leads to dysfunction of another. A complex pathophysiology, cardio-renal syndrome (CRS), has been redefined in recent years.[4] CRS has been described only recently there is limited information about the epidemiology, clinical course, and treatment of this condition. We compared our results with few available studies. The worsening of renal function occurring in patients with heart failure and preserved ejection fraction may belong to CRS type 2. In this syndrome, chronic heart disease and CKD frequently coexist and it can be hardly distinguished which disease came first. In other words, most often CRS type 2 cannot be distinguished from type 4 CRS in which, among chronic heart disease the following conditions should be considered: cardiomyopathy, LV remodeling and dysfunction, diabetic cardiomyopathy. The coexistence of renal impairment in heart failure with preserved ejection fraction (CRS type 2 and 4) is common in older females with hypertension and/or diabetes. The involvement of the kidney may be under-diagnosed in patients with heart failure and preserved LVEF.[8] In our study 50% of patients had diastolic dysfunction with preserved left ventricular systolic function. Renal dysfunction is highly prevalent in patients with heart failure. Worsening of renal function in patients with acute decompensated heart failure (ADHF), impacts the short and long-term morbidity and mortality. Management of patients presenting with ADHF and concomitant renal dysfunction continues to be challenging, due to secondary hyperaldosteronism as well as diuretic resistance in ADHF. Renal function is the single most important prognostic factor in the outcome of patients with ADHF.[9] Similarly about 50% of patients with type 1 CRS in our study presented with ADHF. Nodari S et al Cardio-renal syndrome (CRS) is a renal dysfunction occurring in a large percentage of patients hospitalized with congestive heart failure (HF). Cardiac and renal dysfunctions often occur simultaneously because they share causes and pathogenetic mechanisms. Current therapies for HF are focused on improving myocardial function and hemodynamic balance, but may have potential consequences for worsening renal function. The guidelines about patients with cardio-renal and reno-cardiac syndromes are lacking.[10] Nodari S et al stated that, coexistence of renal impairment in heart failure with preserved ejection fraction (CRS type 2 and 4) is common especially in older females with hypertension and diabetes. Differently from CRS in heart failure with reduced ejection fraction, the involvement of the kidney may be under-diagnosed in patients with heart failure and preserved ejection fraction and the optimal therapeutic strategy in this condition is challenging. Precipitating factors for this CRS are infections and non steroidal inflammatory agents.[10] Similarly in our study pneumonia, urinary tract infections and cellulitis were the precipitating factors for presentation with CRS. In our study total 57 (51.81%) patients were with type 1 CRS (e.g. hypertension, ACS, acute cardiogenic shock or decompensated congestive heart failure), 3 (2.72%) patients had type 2 CRS (e.g. chronic congestive heart failure) causing progressive chronic kidney disease. 9 (10%) patients had type 3 CRS (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction (e.g. heart failure, arrhythmia, ischemia), 11(2.72%) patients had type 4 CRS (CKD) contributing to decreased cardiac function and 30 (27.27%) patients had type 5 CRS (e.g., sepsis) causing both cardiac and renal dysfunction, in our study. Biomarkers can contribute to an early diagnosis of CRS and to a timely therapeutic intervention.[8] CRS type 1 (acute cardiorenal syndrome) and type 3 (acute renocardiac syndrome) are common in the critical care specialist. CRS type 1 is characterized by an acute deterioration in cardiac function that leads to acute kidney injury (AKI); in CRS type 3, AKI leads to acute cardiac injury and/or dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia. CRS type 1 is commonly seen in the coronary care unit and cardiothoracic intensive care unit.[11] In our study total 15 (13.63%) patients presented with coronary artery disease (CAD), 17 (15.45%) patients, with pulmonary edema, 25 (22.72%) patients, with accelerated hypertension with LVF and 3 (2.72%) patients

with cardiomyopathy (type 1 CRS). Total 57 (51.81%) patients with type 1 Cardio-renal syndrome (CRS) and 9 (10%) patients with type 3 CRS with predominance of type 1 CRS. Shah B N et al stated that, the heterogeneity of patients fall under the umbrella term of CRS. They reported a 63-year patient with known severe heart failure and chronic renal impairment, admitted with acute decompensated heart failure (ADHF). Creatinine over the next week and renal function deteriorated significantly (urea 51.1 mmol/L, creatinine 503 mmol/L, eGFR 8) requiring inotropic support and then haemofiltration (type 1 and 3 CRS).[4] similarly, in our study total 11(10%) patients with chronic kidney injury and 17 (15.45%) patients, presented with pulmonary edema secondary to acute decompensated heart failure with scenario suggestive of acute on chronic renal failure. C. Chelazzi et al stated, about 10 to 15% of all patients admitted to ICU develop septic shock. Moreover, numerous studies have shown septic AKI to be highly common among the critically ill, ranging from 16% to 41% of patients with severe sepsis and septic shock (type-3-5). Patients with septic AKI are often older, have a higher prevalence of comorbidity and are more severely ill than those with non-septic AKI. In our study total 30 (27.27%) patients had type 5 CRS.[12] Pavan M et al studied acute reno-cardiac syndrome (cardiorenal syndrome type 3) and its outcome in a suburban population in India. Of 100 patients admitted with AKI type 3 CRS was documented in 29%. Acute gastroenteritis (46%) was the leading cause of acute kidney injury. Cardiogenic pulmonary edema (56%) was the most common cause of acute cardiac dysfunction.[12] Similarly total 9(8.18%) patients, 6 (6.69%) males and 3 (7.31%) females, presented with acute kidney injury (type 3 CRS) secondary to hypotension and hypovolemia. Shah B N et al reported a 31 year man with a two week history of malaise and a 2 day history of hemoptysis with deranged renal function tests with echocardiography revealed moderate global systolic dysfunction indicating probable uraemic cardiomyopathy. A renal biopsy confirmed the diagnosis of glomerulonephritis. After his first three sessions of hemodialysis, echocardiography was repeated and revealed normal systolic function. (type-1-4 CRS).[4] Similarly, in our study 3 (2.72%) patients, 2 (2.89%) males and 1 (2.43%) female, presented with cardiomyopathy with severe LV systolic dysfunction (mean LVEF: 28±3%) and recovered significantly with pharmacotherapy and ultrfiltration. C. Chelazzi et al myocardial dysfunction may occur in up to 20% of patients with septic shock. Patients with myocardial dysfunction have significantly higher mortality (70%) compared to septic patients without cardiovascular impairment (20%) with left ventricular systolic dysfunction. About 30–80% of patients with severe sepsis and septic shock show NSTEMI on ECG with serum troponin values above the normal range.[12] Similarly in our study significant number of patient had type 5 CRS 27.27% secondary to septicemia, urinary tract infection, pneumonia, decompensated liver cirrhosis and cellutitis with mortality rate was high amongst patients with type 5 cardio-renal syndrome ('p' <0.023). Shah B N et al reported a 32 female with end-stage renal failure secondary (CKD) to type 1 diabetes mellitus with transthorasic echocardiography showing concentric ventricular hypertrophy and severely impaired systolic function. After hemodialysis, repeat echocardiography revealed marked improvement in systolic function, with LV dysfunction now only mild rather than severe (Type 4 CRS).[4] Similarly, in our study total 11(10%) patients with chronic kidney injury of them 5 had moderate LV systolic dysfunction which partially improved with ultrafiltration. Pavan M et al reported only 42% of the patients with acute reno-cardiac syndrome (type 3) had complete recovery of kidney function. Requirement of renal replacement therapy was found to be significantly high in patients with acute reno-cardiac syndrome (43% versus 9% in those with AKI and no cardio-renal syndrome) and was associated with high rate of mortality (17%).[13] In contrast to these results all patients with type 3 CRS managed successfully with volume replacement, stepped up pharmacotherapy and only two patients required short term ultrafiltration therapy with no mortality. There is a need for primordial prevention and early intervention on large scale for type-3 CRS. Anan Chuasuwan et al described acute reno-cardiac CRS (type 3) in which acute kidney injury (AKI) results in acute cardiac injury or dysfunction. The mechanisms whereby AKI leads to cardiac dysfunction have been proposed to include two categories: direct effects of AKI on the heart, and effects of AKI on remote organ function with indirect effects on the heart. The high morbidity and mortality is likely a result of this type-3 CRS.[14] In our study 9 (10%) patients with type 3 CRS successfully managed with no mortality. Type 5 CRS refers to secondary cardio-renal syndrome or cardio-renal involvement in systemic conditions. It is a clinical and pathophysiological entity to describe the concomitant presence of renal and cardiovascular dysfunction. Type 5 CRS can be acute or chronic and it does not strictly satisfy the definition of CRS. However, it encompasses many conditions in which combined heart and kidney dysfunction is observed.[14] Similarly in our study total 12(10.90%) patients presented with septicemia, 9(8.18%) patients, presented with urinary tract infection, 7(6.36%) patients, presented with pneumonia and 2(1.81%) patients, presented with decompensated Liver cirrhosis with additionally hepato-renal syndrome fulfilling criteria of type-5 CRS. Shah B N et al quoted a case of 28 year male, with fever hypotension, leucocytosis and acute renal failure. Transthoracic echocardiography revealed severely impaired systolic function. He was diagnosed with septic shock and treated with fluids and broad spectrum intravenous antibiotics. Repeat echocardiography one week

later revealed normal systolic function (type-5 CRS), similarly in our study, total 30 (27.27%) patients had type –5 CRS of them 3 had LV systolic dysfunction which improved over period of two weeks of staring antibiotics.[4] Ronco C et al stated that, cardiorenal syndrome (CRS) type 1 is characterized as the development of acute kidney injury (AKI) and dysfunction in the patient with acute decompensated heart failure (ADHF). There is evidence in the literature supporting multiple pathophysiological mechanisms operating simultaneously and sequentially to result in the clinical syndrome characterized by a rise in serum creatinine, oliguria, diuretic resistance, and in many cases, worsening of ADHF symptoms. The milieu of chronic kidney disease has associated factors including hypertension, diabetes, uremic solute retention, and repeated subclinical AKI events all work to escalate individual risk of CRS in the setting of ADHF. All of these conditions have been linked to cardiac and renal fibrosis.[8] In our study total 57 (51.81%) patients with type 1 cardio-renal syndrome (CRS). Total 15 (13.63%) patients presented with coronary artery disease (CAD), 17 (15.45%) patients, with pulmonary edema, 25 (22.72%) patients, with accelerated hypertension with LVF and 3 (2.72%) patients with cardiomyopathy. Type -1 CRS was outnumbered in our study. Total 15 (27.27%) patients had type-2 diabetes mellitus, 18 (32.72%) patients had hypertension and 12 (21.81%) patients had ischemic heart disease (IHD). Bradley A. Bart et al concluded that, ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Ultrafiltration was inferior to stepped pharmacologic therapy. Ultrafiltration was associated with a higher rate of adverse events.[7] In our study majority of patients underwent stepped intensive pharmacotherapy to treat CRS and those who are non-responding to pharmacotherapy received ultrafiltration therapy. Chiara Lazzeri et al reported that, cardiorenal dysfunction is usually secondary to multiple factors acting in concert (and not only reduced cardiac output). The coexistence of renal impairment in heart failure with preserved ejection fraction (CRS type 2 and 4) is common in older females with hypertension and/or diabetes. The involvement of the kidney may be under-diagnosed in patients with heart failure and preserved LVEF.[1] In our study 50% of patient had diastolic dysfunction with preserved LVEF. The main mechanisms thought to be involved in the pathophysiology of this condition are represented by the increase of intra-abdominal and central venous pressure and the activation of the rennin-angiotensin system. Sarraf M et al stated that, secondary cardio-Renal Syndromes (Type 5) does not have a primary and secondary organ dysfunction, situations do arise where both organs are simultaneously targeted by systemic illnesses, either acute or chronic. Examples include sepsis and diabetes mellitus.[9] Similarly in our study 30 (27.27%) patients with type 5 CRS. Legrand M et al stated that, cardiorenal syndrome has a complex pathophysiology and has a generally poor prognosis in patients with acutely decompensated heart failure (ADHF). In our study out of 9 deaths with CRS only 2 died with type 1 CRS with ADHF who developed STEMI. Addition of biomarkers of renal injury may provide additional prognostic value to biomarkers of renal or cardiac function, but more data are needed. Biomarkers reflecting renal function and injury are likely to better phenotype subgroups of patients with cardiorenal syndrome and to provide unique prognostic information.[15] Early identification of worsening kidney function is essential for early treatment of CRS. Use of biomarkers that become detectable before the traditional tests for kidney function, including GFR or serum creatinine have made to easier. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β- D-glucosaminidase (NAG) and kidney injury molecule 1 (KIM-1) implicated in tubulointerstitial damage are being used to identify acute kidney injury (AKI). Serum cystatin C is elevated earlier than creatinine. Other biomarkers that have proven useful include B-type natriuretic peptide (BNP), interleukin-18 (IL-18) and fatty acid-binding protein (FABP). Tests for volume status and end-organ perfusion are also useful in the diagnosis of CRS. Urine sediment examination should be performed in differentiating CRS from other causes of AKI by excluding pathologic cells, casts or crystals.

CONCLUSIONS

The present study highlighted majority of patient had type 1 cardio-renal syndrome and next to it was type 5. The significant number of patients with cardio-renal syndrome had diastolic dysfunction with preserved left ventricular ejection fraction. Hypertensive heart disease and coronary artery disease with diastolic dysfunction were the most common etiology for type 1 cardio-renal syndrome. Hypertension was the most common clinical finding in cardio-renal syndrome. About one forth of patients with cardio-renal syndrome received intensive pharmacotherapy and one forth received hemodialysis (ultrafiltration) as a treatment modality to treat cardio-renal syndrome. Total one tenth had CKD and one tenth had of patients AKD at the time of presentation (type 3 and 4 CRS). The mortality rate was high amongst patients with CKD (type 4 CRS) and type 5 cardio-renal syndrome. Half of the total population had diabetes mellitus, hypertension and coronary artery disease isolated or together complicating CRS. Infectious etiologies (one fourth) were significant cause of type 5 cardio-renal syndrome in present cohort. The mortality rate was relatively more

with type 4 and 5 CRS compared to type 1, 2 and 3 CRS. The mean creatinine level was significantly high in patients with mortality. Diuretic therapy, vasodialators, inotropic agents and or ultrafiltration should be used judiciously along with treatment of precipitating factors like accelerated hypertension, infection and dehydration. The use of classification of CRS can help physician to categorize the groups of patients, provides the rationale, specific management strategies, risk stratification of the population under treatment. This article highlighted overall incidence, types, etiology, complications, mortality, treatment modality strategies, and outcome aspects of cardio-renal CRS subtypes. Novel biomarkers and therapeutic interventions for primary and secondary disorders are being developed and tested for CRS, which will improve the outcome of CRS in future.

ACKNOWLEDGEMENT

The authors thank the residents for their contribution for managing patients with CRS and in data collection and analysis.

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