



ORIGINAL RESEARCH PAPER

Nephrology

TO IDENTIFY RISK FACTORS FOR PATIENTS OF CARDIO- RENAL SYNDROME IN A TERTIORY CARE HOSPITAL OF NORTH INDIA

KEY WORDS: Risk factors, cardio-renal syndrome, chronic kidney disease

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ABSTRACT

In both developed and developing countries there is a rapidly growing epidemic of non-communicable disease like cardiovascular disease and kidney disease, especially in individuals who are older, obese and with proneness towards diabetes and hypertension. In today's world, doctors are attending patients who have both heart as well as kidney failure, rendering that both the diseases develop concomitantly. This study will help us to understand the risk factors for the development of cardio renal syndrome in Indian population. It will also help in improving the outcome of these patients by increasing the awareness and also by using multidisciplinary approach, with the expertise of cardiology, nephrology and critical care physician.

INTRODUCTION

Cardiovascular disease (CVD), including heart disease and stroke, is the leading cause of death in the United States, regardless of self-determined race/ethnicity (1). Worldwide also it remains one of the leading causes of morbidity and mortality. Furthermore, multiple risk factors significantly contribute to CVD morbidity and mortality, including the constellation of risk factors termed cardiometabolic risk (CMR) CMR refers to interrelated traditional risk factors for metabolic syndrome (MetS) such as dyslipidemia, hypertension, obesity, insulin resistance, and hyperglycemia as well as behavioral factors such as physical inactivity, smoking, and unhealthy eating patterns (2). Chronic kidney disease (CKD) is a worldwide public health problem affecting 10-16% of the adult population (3). In India, given its population >1 billion, the rising incidence of CKD is posing a major problems for both healthcare and the economy. Very often a physician is confronted with patients who have concomitant heart as well as kidney failure. Various epidemiological studies have shown that renal impairment is a common and independent risk factor of morbidity and mortality (4) in patients with cardiac disease, either in asymptomatic (5) or symptomatic (6) congestive heart failure (CHF) patients. Moreover, chronic kidney disease (CKD) plays a significant role in the progression of cardiovascular disease regardless of the status of the heart (7). Death from cardiac causes is 10–20 times more common in patients with CRF than in matched segments of the general population (8). The strong connection between renal and cardiovascular disease has revived interest in the complex interactions between heart and kidneys. The term cardiorenal syndromes (CRS) was coined by Ledoux in 1951 and referred to combined heart and kidney failure (9). Since Indian data is lacking this study will help us to understand the risk factors for the development of cardiorenal syndrome in our population. It will help in developing awareness and will help improve the outcome of these complex patients using a multidisciplinary approach, combining the expertise of cardiology, nephrology and critical care physicians.

AIMS AND OBJECTIVES

To Identify risk factors and predictors for Cardio- Renal syndrome.

MATERIAL AND METHODS

This was a prospective, observational study done to define the incidence of Cardio-Renal syndrome in an inpatient population and to study the complications and disease outcomes of patients presenting with cardiac disease and renal failure.

Inclusion criteria

- All consecutive patients admitted to the Intensive coronary care unit (ICCU) at Christian Medical College and Hospital (CMCH), Ludhiana, during the one year study period between

1st March 2013 till 28th February 2014 were included in the study.

- All patients above the age of 18 years willing to participate in the study after giving prior informed consent were included.

Exclusion Criteria

- Age less than 18 years
- Pregnancy
- Patients unwilling to participate in the study or give informed consent
- Patients discharged against medical advice before a definitive diagnosis is made or three days.

Methodology

The study was conducted in the in-patients admitted to the Intensive Coronary Care Unit of the Cardiac Research Centre at CMC, Ludhiana. All the patients willing to participate in the study were included. Demographic data was collected according to the proforma. History and clinical examination was done and blood and urine samples were collected as per protocol. Blood samples were collected at admission and included complete blood profile, blood urea, creatinine, electrolytes, total protein, albumin and cardiac enzymes. Serum creatinine levels were repeated atleast for three consecutive days and later as per requirement. Daily intake output, blood pressure were recorded till discharge. The patients were studied for etiology, recovery, progression, intervention including hemodialysis, outcome at discharge. Mortality was defined as death during in patient care.

Incidence was estimated from the proportion of confirmed patients with cardio-renal syndrome admitted to ICCU and total number of patients admitted with cardiac diseases during the study period. Patients were described with clinical presentation, laboratory profile and outcome of the disease.

STASTICAL ANALYSIS

The Chi square test, ANOVA and the paired t test was used to determine the risk factors for development of Cardio- renal syndrome.

RESULTS

This study was a one year prospective study done among the inpatient population admitted in Intensive Coronary Care Unit (ICCU) of Christian Medical College and Hospital, Ludhiana. The study period was from 1st March 2013 till 28th February, 2014 During the study period a total of 1524 patients were admitted in ICCU. Among these 126 patients were not found to have a cardiac disease, 26 deaths and 39 patients were discharged against medical advise within first three days, 133 patients did not give consent to participate in the study. All these patients were not included for analysis as per our study proforma

Sex distribution

Table 1 : Sex distribution

Sex distribution	Frequency	Percentage (%)
Females	431	38.41
Males	691	61.59
Total	1122	100.00

Table 1 shows the sex distribution of the study population . There were a total of 1122 patients, out of which 691 (61.59%) were males and 431 (38.41%) were females, with male to female sex ratio of 1.6: 1.

Figure 1

Table 2 : Age Distribution

Age (Years)	Frequency	Percentage (%)
<20	1	0.09
21-30	18	1.60
31-40	56	4.99
41-50	218	19.43
51-60	329	29.32
61-70	306	27.27
71-80	159	14.17
81-90	33	2.94
91-100	2	0.18
Total	1122	100.00

Table 2 shows the distribution of the patients according to their age. Majority of the patients 635 (56.65%) were between 51 to 70 years of age. The mean age of the study population was 59.24 ± 12.22 years. The youngest and oldest patient enrolled were 17 years and 99 years respectively.

Figure 2

Table 3 : Co-morbidities

Co-morbidity	Frequency	Percentage (%)
Diabetes Mellitus	456	40.64
Hypertension	623	55.53
Infection	155	13.81
Chronic Kidney disease	104	9.2

Table 3 shows the presence of various common co-morbidities in our study population. Hypertension was the most common seen in 623 (55.53%) patients. In our study population 456 (40.64%) of the population was diabetic. In 155 (13.81%) there was evidence of infection at time of hospital admission. Chronic Kidney disease was present in 104 (9.2%) .

Table 3 : Presenting symptom

Symptom	Frequency	Percentage (%)
Angina	636	56.68
Dyspnea	437	38.94
Palpitation	213	18.98
Syncope	80	7.1
Orthopnea	42	3.74
Edema	18	1.6

This table 3 shows the distribution of patients on the basis of the various presenting symptoms. The symptoms were seen in various combinations. Angina was the most common symptom seen in 636 (56.68%) of the patients, with dyspnea being the second common symptom seen in 437 (38.94%) of the patients.

RISK FACTORS

Table 4: Sex and Cardiorenal Syndrome

Sex	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	Number	Percentage	Number	Percentage	
Female	211	48.96	220	51.04	431 (100)
Male	325	47.03	366	52.97	691 (100)
Total	536	100.00	586	100.00	1122

p value 0.531

Table 4 shows the incidence of cardio-renal syndrome according to the gender.

In our study population of 1122 patients , cardio-renal syndrome was seen in 586 (52.23%) of the patients . This table depicts that there was no difference in the incidence of cardio-renal syndrome according to the gender.

DIABETES AND CARDIO-RENAL SYNDROME

Table 5: Diabetes Mellitus and Cardiorenal Syndrome

	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total(%)
	No	%	No	%	
Non diabetics	369	55.4	297	44.59	666 (100)
Diabetics	167	36.62	289	63.3	456 (100)
Total	536	47.77	586	52.23	1122 (100)

p value < 0.005.

Table 5 shows the incidence of cardio-renal syndrome among the diabetics in comparison to the non – diabetic population. Out of the total of 1122 patients in our study population, 456 (40.64%) were diabetics. 289 (63.38%) out of the total 456 diabetic patients; developed cardio-renal syndrome whereas among the non diabetic population of 666 only 297 (44.59%) developed cardio-renal syndrome. There was a statistically significant difference in incidence of cardio- renal syndrome between diabetic and non diabetic population with p value being < 0.005 (the odds ratio being 2.150 with 95% CI 1.684-2.745).

HYPERTENSION AND CARDIO-RENAL SYNDROME

Table 6: Hypertension and Cardio-renal Syndrome

Hypertension	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total(%)
	No	%	No	%	
Normotensive	260	52.10	239	47.90	499 (100)
Hypertensive	276	44.30	347	55.70	623 (100)
Total	536	47.77	586	52.23	1122 (100)

P value = 0.009

Table 6 depicts the relationship of hypertension with occurrence of cardio-renal syndrome.Out of the 1122 study population, 623 (55.52%) were hypertensives . There was an increased chance of developing cardio-renal syndrome in patients who were hypertensive in comparison with normotensive population and this difference is statistically significant with p value of 0.009 (with odd's ratio 1.368 with 95% CI 1.080 – 1.732).

INFECTON AND CARDIO-RENAL SYNDROME

Table 7: Infection and Cardio-renal Syndrome

Infection	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total(%)
	No	%	No	%	
Absent	510	52.74	457	47.26	967 (100)
Present	26	16.77	129	83.23	155 (100)
Total	536	47.77	586	52.23	1122 (100)

P value < 0.005

Table 7 shows the occurrence of cardio-renal syndrome in patient presenting with infection. Out of the total 1122 patients,155 (13.8%) had features suggestive of infection at presentation. Among the patients who presented with features of infection, 129 (83.33%) developed cardio-renal syndrome whereas 457 (47.26%) of the patients without evidence of infection developed cardio-renal syndrome. This table shows that presence of infection significantly increases the risk of developing cardio- renal syndrome (p value being < 0.005). Odds ratio being 5.537 with

95% CI 3.567 – 8.596.

ACUTE HEART FAILURE AND CARDIO-RENAL SYNDROME
Table 8: Acute Heart Failure and Cardio-renal Syndrome

Acute Heart Failure (AHF)	Cardio-renal syndrome absent		Cardio-renal syndrome present		Total(%)
	No	%	No	%	
Absent	485	69.29	215	30.71	700 (100)
Present	51	12.09	371	87.91	422 (100)
Total	536	47.77	586	52.23	1122 (100)

P value < 0.0005

Table 8 shows the development of cardio-renal syndrome in patients who are presenting with acute heart failure. This includes patients who presented with acute decompensated heart failure, acute coronary event with acute heart failure. Out of the total of 1122 patients, 422 (37.61%) had features of heart failure at presentation. Among the 422 patients 371 (87.91%) developed cardio-renal syndrome; whereas only 215 (30.71%) of the patients who did not have features of acute heart failure developed cardio-renal syndrome. This shows that presence of acute heart failure at the initial presentation significantly increases the development of cardio-renal syndrome (p value < 0.0005). Odds ratio of 16.140 with 95% CI 11.752 – 2.914.

ARRHYTHMIA AND CARDIO-RENAL SYNDROME
Table 9: Arrhythmia and Cardio-renal Syndrome

Acute Heart Failure (AHF)	Cardio-renal syndrome absent		Cardio-renal syndrome present		Total(%)
	No	%	No	%	
Absent	485	69.29	215	30.71	700 (100)
Present	51	12.09	371	87.91	422 (100)
Total	536	47.77	586	52.23	1122 (100)

P value = 0.03

Table 9 shows the incidence of cardio-renal syndrome according to the presence of arrhythmia. Out of the total 1122 patients 204 (18.18%) had arrhythmia at the time of hospitalization. Among the 204 patients, 126 (61.76%) developed cardio-renal syndrome during hospital stay as compared to 460 (50.11%) out of the total 918 who did not have arrhythmia at presentation. This shows that presence of arrhythmia at the time of hospitalization is a risk factor for development of cardio-renal syndrome (p value 0.03). Odd's ratio of 1.608 with 95% CI 1.179 – 2.194.

SYSTOLIC BLOOD PRESSURE AND CARDIO-RENAL SYNDROME

Table 10 shows the occurrence of cardio-renal syndrome in relation to systolic blood pressure. In our study population 671 (59.80%) of the patients had systolic blood pressure between 100-140 mm of Hg, 133(11.86%) had systolic blood pressure of <100 mm of Hg and 318 (28.34%) had systolic blood pressure of >140 mm of Hg.

Table 10: Systolic Blood Pressure and Cardio-renal Syndrome

Systolic BP (mmHg)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
< 100	21	15.79	112	84.21	133 (100)
100-140	368	54.84	303	45.16	671 (100)
> 140	141	46.23	171	53.77	318 (100)
Total	536	47.77	586	52.23	1122 (100)

P value < 0.005

DIASTOLIC BLOOD PRESSURE AND CARDIO-RENAL SYNDROME
Table 11: Diastolic Blood Pressure and Cardio-renal Syndrome

Diastolic BP (mmHg)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
< 60	8	14.29 %	48	85.71 %	56 (100)
60-90	430	51.07 %	412	48.93 %	842 (100)
> 90	98	43.75 %	126	56.25 %	224 (100)
Total	536	47.77	586	52.23	1122 (100)

Table 11 shows the occurrence of cardio-renal syndrome in relation to diastolic blood pressure at the time of presentation. Out of total 1122 patients, 842 (75.04%) had diastolic blood pressure between 60-90 mm of Hg whereas 56 (4.91%) had diastolic blood pressure < 60 mm of Hg and 224 (19.96%) had diastolic blood pressure > 90 mm of Hg. This table shows that patients presenting with low diastolic blood pressure are at an increased risk of developing cardio-renal syndrome in comparison with those with normal or high diastolic blood pressure.

BLOOD UREA AND CARDIO-RENAL SYNDROME
Table 28: Blood Urea and Cardio-renal Syndrome

Blood Urea(mg/dl)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
< 40	461	65.30 %	245	34.70 %	706 (100)
≥ 40	75	18.03 %	341	81.97 %	416 (100)
Total	536	47.77	586	52.23	1122

P value < 0.005

Table 12 shows the development of cardio-renal syndrome in relation to the admission blood urea. Out of the total 1122 patients, 416 (37.07%) had an admission blood urea of ≥ 40mg/dl. Amongst these patients, 341 (81.97%) developed cardio-renal syndrome in comparison to 245 (34.7%) of the patients who presented with normal serum urea (p value < 0.005).

EJECTION FRACTION AND CARDIO-RENAL SYNDROME
Table 13: Ejection Fraction (EF) and Cardio-renal Syndrome

EF	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
≥ 40 %	481	68.71	219	31.29	700 (100)
< 40%	55	13.03	367	86.97	422 (100)
Total	536	47.77	586	52.23	1122

P value < 0.0005

Table 13 shows the incidence of cardio-renal syndrome in patients with preserved left ventricular ejection fraction versus those with reduced left ventricular ejection fraction (< 40%). It was seen that 422 (37.61%) of the patients had reduced LVEF of < 40%. Amongst the 700 patients with normal LVEF, 219 (31.29%) developed cardio-renal syndrome whereas 367 (86.97%) of the patients with reduced LVEF developed cardio-renal syndrome (p value < 0.0005; odds ratio of 14.65 with 95% CI 10.58-20.29).

CHEST X-RAY AND CARDIO-RENAL SYNDROME

Table 14 shows the chest X-ray findings at presentation to the hospital. Out of the total 1122 patients, 746 (66.48%) has normal chest x-ray on presentation whereas 330 (29.41%) were suggestive of pulmonary edema whereas 46 (4.09 %) has features of pneumonia.

In patients who had pulmonary edema on chest x-ray 294 (89.09%) developed cardio-renal syndrome as compared to 257 (34.45%) of the patients who had normal chest x ray. This was statistically significant difference with p value of < 0.005. This table shows that presence of features of pulmonary edema at the time of presentation predicts the risk of development of cardio-renal syndrome.

Table 14: Chest X-ray and Cardio-renal Syndrome

Chest X-ray (numbers)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
	Normal (746)	489	65.55	257	
Pulmonary edema (330)	36	10.91	294	89.09	330 (100)
Pneumonia(46)	11	23.91	35	76.09	46 (100)
Total	536	47.77	586	52.23	1122

Pvalue < 0.005

Table15: Drugs used and risk of development of Cardio-renal Syndrome

Drugs	Cardio-renal syndrome absent (n=536)		Cardio-renal syndrome present (n=586)		P value	OR (95% CI)
	No	%	No	%		
	Diuretics (n=710)	196	36.5 %	514		
ACE/ARB (n=293)	113	21.08 %	180	30.71 %	0.003	1.660 (1.265-2.178)
Beta blockers (n=566)	334	62.31 %	232	39.59 %	< 0.05	0.396 (0.312-0.504)
Nitrates (n=1005)	479	89.36 %	526	89.76 %	0.82	1.043 (0.711-1.530)
Calcium channel blockers (n=894)	423	78.9 %	471	80.37 %	0.54	1.094 (0.818-1.464)

Amongst the various therapeutic agents used , diuretic (87.75% vs 36.5%, p value of < 0.0005) and ACE/ARB (30.07% vs 21.08%, p value of 0.03) predicted the development of cardio-renal syndrome. The use of beta blockers was (39.59% vs 62.31%) in patients who developed cardio-renal syndrome as compared to those who did not develop cardio-renal syndrome. Whereas use of nitrates and calcium channel blockers was not different between the two groups. The highest odd's ratio for development of cardio-renal syndrome was seen with diuretic use with OR 13.101 with 95% CI (9.650 – 17.784).

SEPSIS AND CARDIO-RENAL SYNDROME

Table 16: Sepsis and Cardio-renal Syndrome

	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	No	%	No	%	
	No sepsis	523	55.29	423	
Sepsis	13	7.39	163	92.61	176 (100)
Total	536	47.77	586	52.23	1122 (100)

Pvalue < 0.005

Table 16 shows that out of the total of 1122 patients , 176 (15.68%) patients fulfilled the criteria of sepsis, with 105 (9.3%) having sputum / ET culture positivity, 66 (5.8%) had blood culture positivity and 5 (0.53%) had urine culture positivity. Out of the 176 patients with sepsis, 163 (92.61%) developed cardio-renal syndrome whereas 13 (7.38%) with sepsis did not develop cardio-renal syndrome (p value being < 0.005).

DISCUSSION

Many patients with heart failure have underlying renal dysfunction, and similarly, patients with kidney failure are prone to cardiac failure. Primary disorders of one of these two organs can cause dysfunction to the other, determining the pathophysiological basis for the cardiorenal syndrome (CRS). Although it was defined and classified several years ago (10) only in 2008 was this syndrome unanimously accepted in a consensus conference by experts in nephrology, critical care, cardiac surgery and cardiology,

under the auspices of the Acute Dialysis Quality Initiative (ADQI) (11). Moreover, mortality, morbidity and cost of care greatly increase when cardiac and renal diseases coexist. Our study was a prospective, observational study conducted at Christian Medical College and Hospital, Ludhiana , during the one year study period between 1st March 2013 till 28th February 2014 . The study was done to define the incidence of Cardio-Renal syndrome in an inpatient population and to study the complications and disease outcomes in these patients. This study was done among the in-patient population admitted in Intensive Coronary Care Unit (ICCU) of Christian Medical College and Hospital, Ludhiana. A total of 1122 patients were enrolled in the study. In our study common co-morbidities included Hypertension, Diabetes mellitus, Chronic kidney disease and Infection. Hypertension was seen in 623 (55.53%) Diabetes in 456 (40.64%) and Chronic Kidney disease was present in 104 (9.2%). Among the various types, cardio-renal syndrome type 1 was the most common, seen in 396 (35.29%) of the total population. CRS type 5 was the second most common seen in 88 (7.84%) of the total study population. About 79 (7.04%) and 23 (2.05%) were CRS type 4 and CRS type 2 respectively. None of the patients had type 3 CRS in our study population. There was a significant incremental increase in the incidence of cardio-renal syndrome with increasing dose of diuretics with 88.15% of patients receiving > 200mg / day and 100% patients receiving > 400 mg /day developed cardio-renal syndrome. CRS is a common but under recognized condition which has a profound prognostic implications and has an adverse effect on both morbidity and mortality of cardiac and renal disease occurring alone. This has been shown in various studies done worldwide. Impaired renal function is consistently found to be an independent risk factor for 1 year mortality in acute HF patients, including those with ST segment elevation myocardial infarction (12). In data from the NHANES II study found CVD prevalence of 4.5%, 7.9%, and 12.9% for patients with eGFR a ≥90, 70-89, and < 70 ml/min/1.73m2, respectively (13). Likewise, in a large population-based cohort found similar graded increases in CVD prevalence and HF, along with higher risk of subsequent cardiac events during follow-up associated with degree of decline in eGFR < 60 ml./min/1.73 m2 (14).

CONCLUSIONS

Cardio-renal syndrome is a common condition in Indian population. In patients with co-morbidities like diabetes mellitus, hypertension, anemia and infection, the incidence of cardio-renal syndrome increases. Colossal use of high dose diuretics especially infusion diuretics, inotropes, angiotensin converting enzyme inhibitor and angiotensin receptor blocker increases the incidence of cardio-renal syndrome. Cardio-renal syndrome not only invariably increases the complication rate and duration of hospital stay but also increases the mortality rate of our Indian population.

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