TO DELINEATE THE INCIDENCE OF CARDIO- RENAL SYNDROME IN PATIENTS ADMITTED TO A TERTIARY CARE INTENSIVE CORONARY CARE UNIT (ICCU) – ORIGINAL ARTICLE

Dr. Blessy Sehgal	Senior Resident, (Nephrology), Department of Nephrology, Christian Medical College & Hospital, Ludhiana
Dr. Timothy Rajamanickam*	Professor & Head, Department of Nephrology, Christian Medical College & Hospital, Ludhiana *Corresponding Author
Dr. Rajan Isaacs	Associate Professor, Department of Nephrology, Christian Medical College & Hospital, Ludhiana

ABSTRACT

With the demographic changes in both developed and developing countries toward individuals who are older, more obese and with proneness towards diabetes and hypertension, increased risk of atherosclerosis, there is a rapidly growing epidemic of non –communicable disease like cardiovascular disease and kidney disease. Very often a physician is confronted with patients who have concomitant heart as well as kidney failure. This study will help us to understand the epidemiology, incidence and risk factors for the development of cardio renal syndrome in Indian population. It will also help in awareness and will improve the outcome of these patients using multidisciplinary approach, assimilating the expertise of cardiology, nephrology and critical care physicians

Introduction

The rising prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is a global medical and epidemiological problem seen both in developed and even in the third world countries. Chronic kidney disease (CKD) is a worldwide public health problem affecting 10-16% of the adult population. 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). In the United states the most rigorous estimates for CKD are based on analysis of National Health and Nutrition Examination Surveys (NHANES). According to this survey, the overall prevalence of CKD in adults in United States is 11.5% which translates 23.2 million people (3). In India, given its population >1 billion, the rising incidence of CKD is posing a major problems for both healthcare and the economy. 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 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 (6).

On the other hand Cardiovascular disease is a profound problem in chronic renal failure (CRF), with 43.6% of all deaths in patients with end-stage renal disease (ESRD) due to cardiac causes (3). About half of ESRD-patients will suffer from myocardial infarction (MI) within 2 years after initiating dialysis therapy, and mortality in these patients is high (7). 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 (8). 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 (9). 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 (10). 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 (11).

Since Indian data is lacking this study will help us to understand the epidemiology, incidence and 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 delineate the Incidence of Cardio- Renal Syndrome in patients admitted to a tertiary care Intensive Coronary Care Unit (ICCU).

MATERIAL AND METHODS

This was a prospective, observational study done to define the incidence of Cardio-Renal syndrome in an inpatient population

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.

For each patient cardiac disease was categorized as per criteria mentioned into acute coronary syndrome, congestive cardiac failure and arrhythmias. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. The diagnosis of Cardio-renal syndrome was made according to the ADQI criteria and patients

were thereafter classified according to the 5 types (12). 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.

STASTICAL ANALYSIS

The incidence of cardio- renal syndrome was estimated from the proportion of confirmed cases of Cardio- renal syndrome divided by the total number of patients admitted in ICCU during the study period. The Chi square test, ANOVA and the paired t test was used to determine the risk factors for development of Cardio- renal syndrome.

RESULTS AND ANALYSIS

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 advice 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. Data collection was not complete for another 78, these were also excluded from the final analysis. 1122 patients were finally included for analysis .The following were the results from the study.

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.

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.

Table 3 : Cardiac diagnosis at admission

Cardiac Diagnosis	Frequency	Percentage (%)
Acute Coronary syndrome (ACS)	570	50.80
Acute heart Failure (AHF)	110	9.80
ACS + AHF	265	23.61
ACS + AHF + Arrhythmia	47	4.19
Chronic Heart disease	40	3.57
Tachy-arrhythmia	55	4.90
Brady-arrhythmia	35	3.12
Total	1122	100.00

Table 3 shows the distribution of patients on the basis of their admitting cardiac diagnosis. Acute Coronary syndrome (ACS) was the most common admitting diagnosis. Out of the 1122 patients, 882 (78.60 %) had ACS alone or in combination of acute heart failure and arrhythmias.

Table 4 : Admission estimated Glomerular filtration rate (eGFR)

eGFR (ml/min/ 1.73 m²BSA)	Frequency	Percentage (%)
< 15	31	2.76
15 - 29	87	7.75
30- 59	249	22.19
60-89	389	34.67
≥90	366	32.62
Total	1122	100.00

Table 4 shows the distribution of admission eGFRin our study population. The mean eGFR in this study population was73.89 ± 31.94 ml/min. The maximum e GFR being 191.1 ml/ min / 1.73 m2 body surface area and minimum being 3.9 ml/ min / 1.73 m² body surface area.

Table 5: Incidence of Cardio-renal syndrome

Cardio- renal syndrome	Frequency	Percentage
Absent	536	47.77
Present	586	52.23
Total	1122	100.00

Table 5 shows the incidence of cardio- renal syndrome in the study population. According to this table out of the total 1122 study population, cardio- renal syndrome was seen in 586 (52.23 %) of the patients.

Table 6 : Types of Cardio-renal syndrome

Types of Cardio- renal syndrome (CRS)	Frequency	Percentage (%)
Absent	536	47.77
CRS type 1	396	35.29
CRS type 2	23	2.05
CRS type 4	79	7.04
CRS type 5	88	7.84
Total	1122	100.00

Table 6 shows the frequency of various types of Cardio-renal syndrome in the study population. In our study out of the total 1122 patients, cardio- renal syndrome was seen in 586 (52.23%). Cardio-renal syndrome type 1 was the most common, seen in 396 (35.29%) of the total population.

Table 7 : Arrhythmia and Cardio-renal Syndrome

Arrhythmia	Cardio-renal syndrome Absent		Cardio- renal syndrome Present		Total (%)
	Number	Percentage	Number	Percentage	
Absent	458	49.89	460	50.11	918 (100)
Present	78	38.24	126	61.76	204 (100)
Total	536	47.77	586	52.23	1122(100)

P value = 0.03

Table 7 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.

Table 8: Serum Creatinine and Cardio-renal Syndrome

Serum creatinine (mg/dl)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	Number	Percentage	Number	Percentage	
< 1	385	76.39	119	23.61	504 (100)
1-1.5	148	35.41	270	64.59	418 (100)
1.6-2.0	3	3.85	75	96.15	78 (100)
2.1-3.0	0	0.0	66	100.0	66 (100)
>3.1	0	0.0	28	100.0	28 (100)

> 4.1	0	0.0	28	100.0	28 (100)
Mean	0.86 ± 0.19		1.68 ± 1.36		
Total	536	47.77	586	52.23	1122

P value < 0.005

Table 8 shows the development of cardio-renal syndrome with different levels of admission serum creatinine. This table shows 119 (23.61%) of the patients with admission creatinine of < 1mg% developed cardio-renal syndrome whereas 100% of all the patients with admission creatinine of > 2mg% developed cardio-renal syndrome. The p value was < 0.005 and was statistically significant.

Table 9 : eGFR at admission and Cardiorenal Syndrome

Admission eGFR (ml/min/ 1.73 m2)	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	Number	Percentage	Number	Percentage	
< 15	0	0.0	31	100.0	31 (100.0)
15-29	0	0.0	87	100.0	87 (100.0)
30-59	25	10.04	224	89.96	249 (100.0)
60-89	229	58.87	160	41.13	389 (100.0)
> 90	282	77.05	84	22.95	366 (100.0)
Mean	92.68 ± 23.56		56.71 ± 28.77		
Total	536	47.77	586	52.23	1122

Table 9 describes the incidence of cardio-renal syndrome according to different levels of admission eGFR, as evident from this table, the incidence of developing cardio-renal syndrome was 22.95% in patients with eGFR ≥90ml/min, whereas all the patients with eGFR of less than 30ml/min developed cardio-renal syndrome. This difference was statistically significant.

Table 11: Cardio-renal Syndrome and Outcomes

Outcomes	Cardio-renal syndrome Absent		Cardio-renal syndrome Present		Total (%)
	Number	Percentage	Number	Percentage	
Death	1	1.69	58	98.31	59 (100)
Not recovered baseline	18	5.94	285	94.06	303 (100)
Recovered baseline	517	68.02	243	31.97	760 (100)
Total	536	47.77	586	52.23	1122 (100)

P value < 0.005

Table 10 shows the outcomes in the two groups of patients. the three major outcomes in our study was death seen in 59 (5.25%) of the total population, complete renal recovery seen in 760 (67.73%) of the total study population. 303 (27%) of the patients did not recovered baseline at discharge.

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) (13). Although it was defined and classified several years ago, 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) (14) . 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. 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: 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. 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%). Acute Coronary syndrome (ACS) was the most common admitting diagnosis. Out of the 1122 patients, 882 (78.60 %) had ACS alone or in combination of acute heart failure and arrhythmias. Acute heart failure was the second most common admitting diagnosis, seen in 110 (9.80%), Tachy-arrhythmias and Brady-arrhythmias were seen in 55(4.90%) and 35 (3.12%) of the patients respectively.

The mean admission creatinine was 1.29 ± 1.07 mg/dl with only 504 (44.92%) of the patients having admission serum creatinine levels < 1 mg/dl. The mean eGFR in this study population was 73.89 ± 31.94 ml/min with only 366 (32.62%) had a normal eGFR at the time of presentation to the hospital. Out of the total 1122 study population, cardio- renal syndrome was seen in 586 (52.23 %) of the patients. 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 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). 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 at the initial presentation significantly increases the risk of development of cardio-renal syndrome (p value < 0.0005). Odds ratio of 16.140 with 95% CI 11.752 – 2.914.

CONCLUSIONS

Cardio-renal syndrome is a common condition in our population. Its incidence increases with presence of co-morbidities like Diabetes mellitus, hypertension, anemia and infection. Use of high dose diuretics especially infusion diuretics, inotropes, Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker increases the incidence of cardio-renal syndrome. Occurrence of cardio-renal syndrome significantly increases the mortality. It also increases the complication rate and duration of hospital stay.

REFERENCES
1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB et al. Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation 2012; 125(1):e2–e220.
2. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al: Lipoprotein management in patients with CMR: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008; 51(15): 1512–24.
3. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. USRDS 1997 Annual Data Report. Bethesda, MD, USA: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1997. http://www.usrds.org/adr_1997.htm (11 November 2003).
4. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000; 102(2): 203–10.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327(10): 685–691.
The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left

ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325(5): 293–302.

6. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 2003; 41(1): 47–55.

7. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998; 339(12): 799–805.

8. Ledoux P. Cardiorenal syndrome (in French). Avenir Med 1951; 48(8): 149–53.

9. Goldberg A, Hammerman H, Petcherski S, ZdorovyakA, Yalonetsky S, Kapeliovich M et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. Am Heart J 2005; 150(2): 330–7.

10. Muntner P, He J, Hamm L, Loria C, and Whelton PK . Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13(3): 745-53.

11. Go AS, Chertow GM, Fan D , McCulloch CE and Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305

12. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. J Am Coll Cardiol 2008; 52(19): 1527–39.

13. Isles C. Cardiorenal failure: pathophysiology, recognition and treatment. Clin Med 2002; 2(3): 195–200

14. Ronco C, McCullogh P, Anker SD, Anand I, Aspromonte N, Bagshaw SM et al. Cardiorenal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010; 31(6): 703-11.