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INCIDENCE, PREDICTORS AT ADMISSION, AND IMPACT OF WORSENING RENAL FUNCTION AMONG CARDIOVASCULAR PATIENTS

Aswathy Jai Kumar*, Thomas Zacharia, Anju Joseph, Anu J. and Anu Philip

Department of Pharmacy Practice, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu.

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***Corresponding Author**
Aswathy Jai Kumar
Department of Pharmacy Practice, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu.

ABSTRACT

Cardiovascular disease is a class of diseases that involves the heart, the blood vessels or both. The heart and the kidneys are involved in maintaining hemodynamic stability and organ perfusion through an intricate network. Thus, in patients with cardiovascular diseases, due to reduced renal perfusion, it is common to encounter worsening of renal function during the length of hospital stay. This study was carried out to determine the association between patient's characteristics and the development of worsening renal function, to identify its independent predictors and to assess the relative risk of cardiovascular patients developing worsening renal function using a risk score. After analyzing the data collected, Ejection Fraction was found to be a major risk factor and predictor and a slight decrease in it could increase the likelihood of worsening renal function up to 3 times. Also a risk score was proven to be beneficial in distinguishing the relative risks of developing worsening renal function, ranging from 13% to 67% among different cardiovascular patients. This study reveals that worsening renal function occurs frequently among hospitalized cardiovascular patients and that clinical characteristics available at hospital admission can be used to identify both the predictors and the patients at increased risk for developing worsening renal function.

KEYWORDS: Cardiovascular disease, Worsening renal function, Ejection Fraction.

MATERIALS AND METHODS

This study was carried out in a 700 bedded multispecialty tertiary care private corporate hospital. This Prospective observational study was conducted among 60 patients for a

duration of 6 months between December 2014 and May 2015 and was carried out after obtaining the consent from the hospital authorities and the patients.

Inclusion criteria

Cardiovascular patients of either sex admitted in the study site during the study period and willing to participate.

Exclusion criteria

Patients with insufficient data, critically ill, having prior history of renal failure, pediatric patients (below 18 years of age) as well as pregnant women and patients who are not willing to participate are excluded from the study.

The principal outcome was worsening renal function (WRF), defined as an increase in serum creatinine of >0.3 mg/dl from admission, consistent with several previous investigations. Patients with worsening renal function were identified based on laboratory data and clinical evaluation. Verbal consent was obtained from each subject before initiating the study. Structured preform were used to collect various clinical and demographic details of the patient such as age, gender, length of hospital stay, primary diagnosis, serum creatinine, urea, uric acid, creatinine clearance and ejection fraction. Treatment data including prescribed drugs, dosages and frequency were also recorded. These data were then assessed.

A bivariate analysis was done to determine the association between patients' characteristics and the development of WRF. Independent predictors of WRF were identified using multivariable Cox regression models with stepwise selection method.

Further to assess the prognosis of WRF in Cardiovascular patients, a risk score was calculated. The relationship between this risk score and WRF was evaluated using the Cochran- Armitage trend test to assess significance of the trend. This score gives the relative risk of the patients in developing WRF during the course of their stay.

RESULTS

Patient baseline characteristics are listed in Table 1. Mean age (±SD) of the study population was 55.7±15.9 years. Nearly half the total population was male with a frequency of 49(80.3%), while the remaining 12(19.7%) were female. 59% of the subjects were found to be smokers and 44.3% alcoholics. Demographic details of these patients are shown in Table 2. 32 patients out of 61 were showing normal Ejection Fraction (EF) (52.5%) and EF

dysfunction was shown by 29(47.5%) of the subjects (Table 1). At presentation, the major diagnoses were Hypertension (96.77%), Ischemic Heart Disease (83.87%) and Diabetes mellitus (64.51%) [Fig 1](Table 3).

Majority of the drugs prescribed were Anti Hypertensive drugs (16.02%), Anti coagulants/Anti platelets (10.61%) and antibiotics (10.23%) [Fig 2](Table 4).Worsening renal function occurred in 18 patients (29.5%)[Fig 3].

Out of the 61 patients studied only 29(48%) showed EF dysfunction, while among the WRF patients 16(89%) showed EF dysfunction (Table 1). Similarly hypertension was shown by 61% of the WRF population. Both are major risk factors for WRF.

A bivariate analysis was done to assess the association between patient's characteristics and the development of WRF. The study proved to be significant with the Ejection Fraction being identified as a risk factor for WRF in CVD patients; with a p value of 0.000(Table 1).

Independent predictors of WRF were identified using multivariable Cox regression models with stepwise selection method. The predictors were thus seen to be Ejection Fraction and Hypertension with the study being significant ($p<0.05$).It was statistically proven that with even a slight decrease in EF there could be a likelihood of WRF occurring 3 times more in CVD patients.

Furthermore, a history of HF, pharmacologically treated diabetes mellitus, admission creatinine and elevated systolic BP (>160 mm Hg) were the factors most strongly associated with WRF.[1] In addition, admission creatinine≥1.5 mg/dl and<2.5 mg/dl; as well as ≥2.5 mg/dl were associated with incremental risk. Table 5 indicates these independent risk factors for WRF. A risk score for WRF was devised based on these risk factors.[1]

Points were assigned to each risk factor listed in Table 6. One point was assigned to history of HF, history of diabetes mellitus, and systolic BP >160 mm Hg at admission. Two points were assigned to creatinine 1.5 to 2.4 mg/dl, and three points were assigned to creatinine 2.5 mg/dl. Table 4 shows the relationship between risk score and WRF. It gives the relative risk of each group of patients developing WRF.

The 5% of the total sample population with a risk score of≥4 had a 67% likelihood of developing WRF compared with only a 13% risk among the 25% of the population with a

risk score of 0($p<0.05$ for the trend). Relative to the group of patients with a risk score of 0, the group of patients with score 3 had approximately twice the likelihood of developing WRF (see "relative risk" column in Table 5). Compared with those with risk score of 0, the group with risk score 1 had approximately the same risk of developing WRF, while those with score 2 had approximately 4 times the likelihood of developing WRF. The group with risk score 4 had 5 times the risk.

TABLE 1: BASELINE CHARACTERISTICS OF HEART FAILURE PATIENTS AND WRF

			WRF				
	Total(61)		No(43)		Yes(18)		
	#	%	#	%	#	%	p value
Demographics							
Age: mean (SD)	55.07	15.9					0.989
Male	49	80.3%	35	57.4	14	23.0	0.746
Female	12	19.7%	8	13.1	4	6.6	
Smoker	36	59.0	11	61.6	7	38	0.432
Alcoholic	27	44.3	8	44.4	10	55	0.559
Ejection fraction							
Normal(LVEF ≥50)	32	52.5	2	11.1	16	88.8	**0.000***
EF dysfunction(50 <LVEF)	29	47.5	16	88.8	2	11.1	**0.000***
Medical history							
Prior heart failure	28	45.9	9	50	8	44	0.883
Hypertension	34	55.7	7	38	11	61	0.585
Atrial fibrillation	7	11.5	15	83	3	16.6	0.410
Diabetes Mellitus	29	47.5	10	55.5	8	44	0.754
Stroke	2	3.3	17	94.4	1	5.5	0.518
Myocardial infarction	5	8.2	15	83	3	16.6	0.119
Angina	5	8.2	16	88.8	2	11.1	0.591

TABLE 2: DEMOGRAPHICS DATA

S.No	Parameters	Values
1.	N	61
2.	Mean age	55.7±15.916
3.	Male	49(80.3%)
4.	Female	12(19.7%)
5.	Mean Creatinine	1.55 ± 0.802
6.	Mean weight	69.94±1.06
7.	Mean Urea	42.45± 22.95
9.	Mean Creatinine clearance	62.503±22.22

TABLE 3: CLINICAL CONDITIONS OF PATIENTS (N = 31)

S.No	Clinical conditions	No. of patients	Percentage (%)
1.	Hypertension	30	96.77
2.	Ischemic Heart Disease	26	83.87
3.	Diabetes mellitus	20	64.51
4.	Left ventricular Dysfunction	16	51.61
5.	Renal Impairment	11	35.48
6.	CAD	9	29.03
7.	MI	9	29.03
8.	Chronic obstructive pulmonary disease	8	25.80
9.	Mitral Stenosis	6	19.35
10.	Congestive heart failure	5	16.12
11.	Pulmonary arterial hypertension	5	16.12
12.	Acute Pulmonary Edema	4	12.90
13.	Atrial Fibrillation	4	12.90
14.	CHF	4	12.90
15.	Congestive cardiac failure	4	12.90
16.	Angina pectoris	3	9.67
17.	Dyslipidemia	3	9.67
18.	LRTI	3	9.67
19.	Acute gastroenteritis	2	6.45
20.	Acute myocardial wall infarction	2	6.45
21.	Dilated Cardiomyopathy	2	6.45
22.	Trivial AR	2	6.45
23.	Anemia	1	3.22
24.	Atypical Chest Pain	1	3.22
25.	Diabetic neuropathy	1	3.22
26.	Hypertensive urgency	1	3.22
27.	Hyperurecemia	1	3.22
28.	Hypothyroidism	1	3.22
29.	Stroke	1	3.22
30.	Supraventricular tachycardia	1	3.22
31.	Triple vessel disease	1	3.22

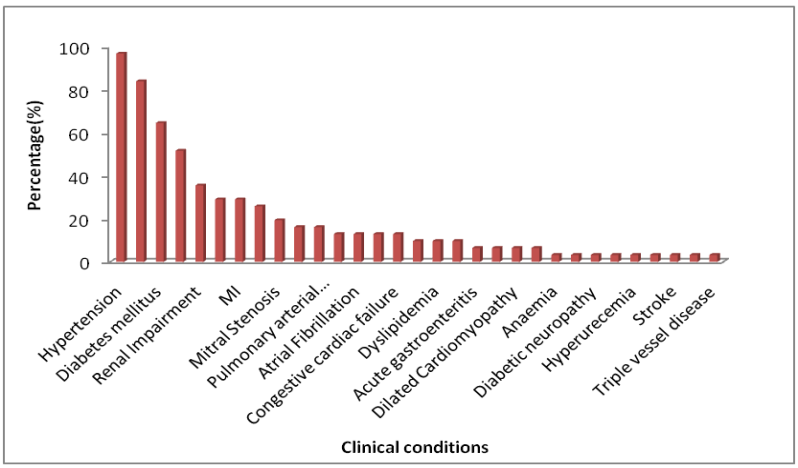

Fig 1: The distribution of the different clinical conditions among the patient population. Values are expressed as percentage.

TABLE 4: PRESCRIBING PATTERNS OF DRUGS IN CARDIOVASCULAR PATIENTS (N = 518)

S. No.	Category	Total drugs	Percentage (%)
1.	Anti hypertensives	83	16.02
2.	Anti coagulants/Anti platelets	55	10.61
3.	Antibiotics	53	10.23
4.	Diuretics	52	10.03
5.	Proton Pump Inhibitors	47	9.07
6.	Vitamins and minerals	35	6.75
7.	Dyslipidaemic agents	32	6.17
8.	Anti diabetics	25	4.82
9.	Anti asthmatic/Bronchodilators	21	4.05
10.	Anti angina	18	3.47
11.	Cardiac glycosides	14	2.70
12.	NSAIDS	13	2.50
13.	Anti anxiety/Anxiolytics	12	2.31
14.	Anti arrhythmic	11	2.12
15.	Anti emetics	9	1.73
16.	Anti gout	8	1.54
17.	Anti convulsants	5	0.96
18.	Miscellaneous	3	0.57
19.	Mucolytics and antitussives	3	0.57
20.	Anti ulcer	2	0.38
21.	Probiotics	2	0.38
22.	Corticosteroids	2	0.38
23.	Renal Protectant	2	0.38
24.	Anti histamine	2	0.38
25.	Anthelmintics	2	0.38
26.	Anti histamines	2	0.38
27.	Thyroid drugs	2	0.38
28.	Anti diarrhoeals	2	0.38
29.	Neurotonics	1	0.19

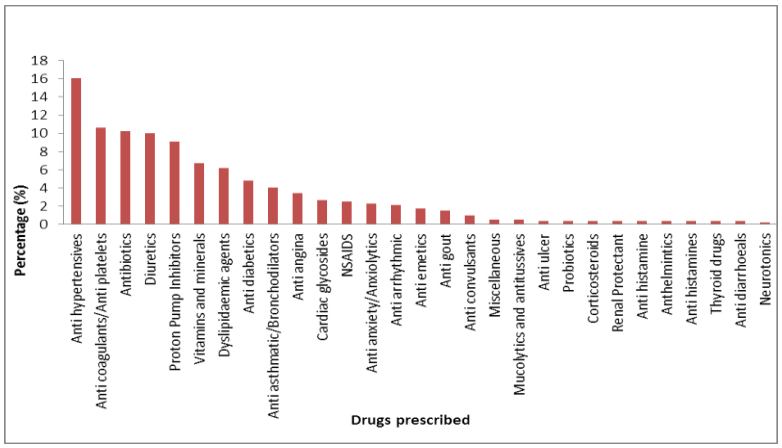

Fig 2: Prescribing patterns of all the drugs used by the CVD patients in this study. Values are expressed in terms of percentage.

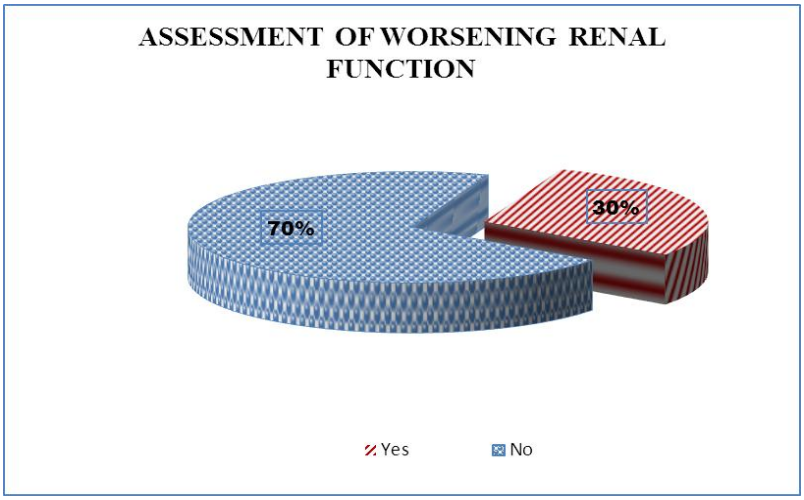

Fig 3: The ratio of worsening renal function in the study population, expressed in terms of percentage.

TABLE 5: INDEPENDENT RISK FACTORS FOR WRF

	Frequency	Percent	Valid Percent	Cumulative Percent
No criteria	15	24.6	24.6	24.6
History of prior CHF+Diabetes+SBP 160	10	16.4	16.4	41.0
1.5 < creatinine <2.5	23	37.7	37.7	78.7
Creatinine>2.5	10	16.4	16.4	95.1
History of prior CHF+Diabetes+SBP160+ Creatinine >2.5	3	4.9	4.9	100.0
Total	61	100.0	100.0	

TABLE 6: Risk score that gives the risk of CVD patients developing WRF

	Total		WRF		Relative Risk
Score	#	%	#	%	
0	15	24.6	2	13.3	1
1	10	16.4	1	10.0	0.75
2	23	37.7	11	47.8	3.59
3	10	16.4	2	20.0	1.5
4+	3	4.9	2	66.7	5
Cochran-Armiage trend test (pvalue<0.05)					
Total	61	100	18	29.5	

DISCUSSION

The present study adds to the growing evidence that WRF is common among patients hospitalized for HF. The principal findings are: 1) 29.5% of patients develop WRF, as defined by serum creatinine increase ≥ 0.3 mg/dl, a previously identified threshold associated

with worse outcomes; 2) baseline characteristics are associated with the development of WRF 3) Ejection fraction and Hypertension are major predictors for WRF and a score derived by weighing independent variables is highly predictive for WRF in CVD patients. The risk associated with post-admission WRF was first reported in a study limited to older HF patients (mean age 79 ±8 years; 44% age over 80 years) that showed a similarly high incidence of WRF (28%).[2] Both the previous and the present studies demonstrate that WRF occurs early, appearing here within the first 3 days in 72% of the patients.

The early occurrence of WRF in the course of hospitalizations for cardiovascular patients suggests that renal deterioration is related to inherent mechanisms of disease or to the impact of therapy administered upon admission, rather than to progressively worsening clinical status over prolonged hospitalization. The mechanisms responsible for WRF are complex and not well-defined. Co-morbid conditions or the treatments utilized may also play a critical role in the development of WRF. It was found that nearly half the total population was male most of them in their late adulthood (51-65 yrs) with 59% of the subject's smokers and 44.3% alcoholics. Only 52.5% of the patients showed normal EF. Majority of the patients were diagnosed with Hypertension. So, it follows that majority of the drugs given to the patients were also Anti Hypertensive (16%).

The associations between patient's baseline characteristics and the development of WRF were assessed by means of bivariate analyses. It was found that Ejection Fraction is a risk factor for WRF with the study being significant (p value<0.05). Ejection fraction (EF) is the fraction of outbound blood pumped from the heart with each heartbeat. Essentially, it is the cardiac output. Hence this study shows significant correlation between renal deterioration and cardiac output. This statement is supported by similar studies which also identify EF as a risk factor of WRF.[3][4]

Intuitively, hemodynamic abnormalities, such as hypotension or low cardiac output, might be expected to play a role in WRF.[5] However, hypotension was uncommon in this population, and, in fact, it was hypertension that emerged as a predictor of WRF. A similar inference has been seen in other studies.[6] It is noteworthy that EF was a predictor of WRF. Small changes in Ejection Fraction can result in adverse effect on worsening renal function in CVD patients; a minor decrease of EF can increase the likelihood of WRF by almost 3 times.

In the study by Daniel et al[7] 27% of the population showed WRF, while in our study 29.5% show WRF. Multivariable analysis identified four clinical parameters present at admission (history of pre-existing HF, diabetes mellitus, admission creatinine of ≥1.5 mg/dl, admission systolic BP >160 mm Hg) that are strongly and independently associated with WRF. Notably, age was not associated with WRF in this study population, indicating that age-related systemic effects are not specifically related to the onset of WRF.

A simple score based on these admission variables distinguished risks of developing WRF ranging from 13% to 67% among different HF patients. According to Daniel E et al[1], patients with higher point totals were more likely to develop WRF. In our study, this is true in case of patients with scores ≥4 as they show a risk of developing WRF 5 times more compared to patients with 0 score. Furthermore, Shagun S et al[11] in their study showed that renal dysfunction is strongly associated with an increased risk of adverse outcome in CVD patients. Also, out of the 61 patients studied only 29(48%) showed EF dysfunction, while among the WRF patients 16(89%) showed EF dysfunction. Similarly hypertension was shown by 61% of the WRF population. EF is both a major risk factor and predictor for WRF, while Hypertension was found to be only a risk factor for WRF.

Although it is recognized that renal function may be more accurately assessed using calculated creatinine clearance, it is also relevant that 24-h urine collection is more cumbersome and costly and lends itself less readily to serial measurement. The strength of this investigation is that the simpler and more readily available measurement of serum creatinine provides a powerful tool for predicting adverse outcomes. The previous report by Weinfeld et al[14] studying renal function and cardiovascular diseases highlights these methodological differences. Those investigators used creatinine clearance rates as well as serum creatinine to assess renal performance among HF patients. Patients with reduced creatinine clearance rates were more likely to develop aggravated renal deterioration and poor outcomes despite similar baseline creatinine level. Nonetheless, our study provides firm support for using increases in serum creatinine to predict adverse outcomes regardless of "actual" renal function. Furthermore, serum creatinine levels are less expensive than assessments of creatinine clearance and they are more clinically useful for monitoring short-term fluctuations in renal function.

Whether 0.3 mg/dl increases in serum creatinine is the best gradation of renal deterioration is also controversial. Some investigators have used a rise in serum creatinine above a threshold

to define renal insufficiency (e.g., creatinine >2.5 mg/dl) or a percentage increase from baseline (e.g., >25% increase), or a combination of these factors.[14] In the current investigation, we utilized a predetermined definition of an increase in creatinine >0.3 mg/dl from admission based on observations in prior studies.[2][15][16] Notably, this definition of WRF enables us to show that WRF is associated with adverse outcomes even in subjects whose peak serum creatinine was <2.5 mg/dl.

CONCLUSION

This study demonstrates that worsening renal function occurs frequently in hospitalized cardiovascular patients. After assessing the demographic and baseline data obtained, it was found that 29.5% of the study population developed WRF.

After analysis of various factors including demographics, medical history, admission characteristics and lab values, association between WRF and Ejection Fraction were found to be significant. It is concluded to be a major risk factor for WRF.

Furthermore, both EF and Hypertension were found to be significant predictors of WRF in the patient population. Relatively small changes in Ejection Fraction have adverse effect on worsening renal function in CVD patients (may increase likelihood of developing WRF by three times). Also, a score derived by weighing independent variables was found to be highly predictive in deriving the relative risk for WRF in CVD patients.

Additional research is required to better delineate in-hospital factors that may precipitate WRF. Furthermore, it will be important to determine whether WRF is itself the cause of increased morbidity and mortality in these patients and therefore, a potential target for intervention, or if WRF is simply a marker of patients with more severe pathophysiologic derangements.

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