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ORIGINAL RESEARCH

Acute kidney injury in patients hospitalised with acute decompensated heart failure

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ABSTRACT

Background
Cardiorenal syndrome (CRS) is not a newly discovered syndrome. The adverse outcomes of the renal impairment in patients with Heart failure were known since long. Our aim in this study was to evaluate the occurrence of AKI, to determine the outcome (morbidity and mortality) in patients suffering with AKI.

Methods
The present observational prospective study was conducted for a duration of 1 yearamong 100 patients (age 18 years or more) admitted to hospital with acute decompensated heart failure.A written informed consent taken from each patient and were then screened for cardiac dysfunction by a detailed history, clinical examination and echocardiography.Univariate logistic regression was used to find out association of various outcomes with AKI. A p value of <0.05 was considered statistically significant.

Results
The mean age of the study population was 58.98 ± 17.16 years. The mean Boston criteria for the population was 9.87 ± 1.36. Baseline S. creatinine, eGFR and even B. Urea were strongly associated with the occurrence of AKI. Presence of diastolic dysfunction was associated with AKI. Mortality and readmission were significantly higher in AKI group as compared to non-AKI group.The predictive value of AKI was maximum with the baseline S. creatinine.

Conclusion
Cardio-renal syndrome is a commonly seen in patients admitted in hospital. AKI can lead to poor cardiac output or pre-renal failure as a result of overuse of diuretics. The mechanism involved is complex. AKI in patients admitted with ADHF has poor prognosis with increased mortality and longer duration of hospital stay.

Keywords: Acute kidney injury, acute decompensated heart failure, prospective study, diabetes, adult.

INTRODUCTION

At present 2% of adult population is affected by HF,[1]resulting in more than 1 million annual hospital admission in the world. The interaction between heart and kidney disease has been an area of considerable interest in years.

Dysfunction of one organ often leads to a deterioration of function of the other one. These patients are grouped together as Cardiorenal syndrome (CRS). Recently, a new definition of CRS has been accepted and it includes a classification of the syndrome into 5 separate subtypes.[2] Between 14-34% of patients with Acute Decompensated Heart Failure (ADHF) develop worsening of renal function.[3] Baseline chronic kidney disease (CKD), diabetes, prior heart failure, and initial presentation with hypertension are established risk predictors for CRS type 1. Decline in renal function after hospitalization for Acute heart failure is frequently observed and has been a predictor of longer hospital stay and increased mortality and morbidity among the patients.

The most common cause of AKI is acute decompensated heart failure (9.8%), Chronic decompensated heart failure (38.2%), Cardiac arrest (11.8%), Myocardial infarction (19.5%), CABG (4.9%), Cardiac valve implantation (5.7%), Heart transplantation (1.6%) and Aortic aneurysm (8.5%).

Acute coronary syndrome (ACS) may induce AKI through various mechanisms. Even a minimal increase in serum creatinine (S.Cr) has been associated with an increased risk of end-stage renal disease and all-cause short and long-term mortality, regardless of whether partial or full recovery of renal function occurred at the time of discharge.[4,5,6]

Around 20% of patients hospitalized with acute myocardial infarction in the USA will develop AKI, which can be partly or completely irreversible.[7] The available data indicate that a baseline S.Cr should be obtained early after admission for ACS and to be closely monitored during hospitalization, which allows early identification of patients at risk of AKI and permits the use of renal protective measures, such as, pre-procedural hydration, limiting contrast volume, use of iso-osmotic contrast agents, and avoiding nephrotoxic medications.[8,9]

Due to the difficulty in diagnosis and treatment of the conditions pertaining to both these organs, Ronco et al.,[2] observed that a more articulated definition in terms of clinical presentation, patho-physiology and diagnosis, and management is needed to explore the complex nature of CRS and its different clinical subtypes based on the recent advances in basic and clinical sciences which have improved our understanding of organ crosstalk.

CRS is not a newly discovered syndrome. The adverse outcomes of the renal impairment in patients with Heart failure were known since long. However, enough literature is not available, at least in our country, for proper understanding of syndrome. The complexity of this syndrome presents a key challenge for singular diagnostic or treatment approaches.

Our aim in this study was to evaluate the incidence of AKI in patients admitted with acute Decompensated Heart Failure, to assess severity of disease and to determine the outcome (morbidity and mortality) of patients suffering Acute Kidney Injury.

MATERIALS and METHODS

Study setting and design

The present observational prospective studywas conducted under the department of medicine and CCU, Dr Baba Saheb Ambedkar Hospital and Medical College for a duration of 1 year (April 2020 to March 2021).

Sample size and study population

The present study included patients (age 18 years or more) admitted to hospital with acute decompensated heart failure.On the basis of previous study, incidence of acute kidney injury in patients with acute decompensated heart failure was 41.7%. Taking this value as reference,

the minimum sample size with 10% margin of error and 5% level of significance is 94 patients. So, to reduce margin of error, total sample size taken is 100.[10] Formula used is: $N = (p\ (1-p)/\ (\ ME/Z_a\ )^2$, where Z_a is value of Z at two sided alpha error of 5%, ME is margin of error and p is incidence rate. The patient with chronic kidney disease, hypovolemia, recent intake of known nephrotoxic drugs and radiocontrast agents were excluded from the study.

Data collection

A written informed consent was explained and taken from each patient before inclusion in this study. The patients were then screened for cardiac dysfunction and patient information was recorded on a pre-structured proforma which included detailed history (demographics, presenting complains, past history of MI, Diabetes, Hypertension, smoking, PVD, H/O any intake of nephrotoxic drugs or material), findings of clinical examination **(**Weight, Height, BMI, HR, Systolic and diastolic blood pressure, JVP, wheeze, crackles, edema, third heart sound), echocardiography (for Ejection Fraction and presence/ absence of diastolic dysfunction), ECG, Chest X-RAY, kidney function test (blood urea, serum creatinine and eGFR), electrolytes, Haemoglobin, trop-T, baseline SpO2. Serial sampling at every 24 hrs for 72 hrs for KFT was done.

Acute Kidney Injury was defiend as increase in S.Cr $\geq$ 1.5 times from the baseline or an absolute rise of S.Cr of 0.3 mg/dl or urine output $\leq$ 0.5 ml/kg/hr for 6 hrs.[11]Acute decompensated heart failure was defined asnew onset of symptoms, signs and objective evidence of HF or acute worsening in severity of chronic heart failure.[12]Boston criteria was utilized for diagnosis of ADHF and AKI were classified on the basis of severity of AKI based on the staging of AKIN(Acute Kidney Injury Network) criteria.[13]Patient having AKI based on the criteria below are identified as cardiorenal syndrome. Kidney function of patients were evaluated 24 hourly for 72 hrs.Patients were evaluated after 90 days of admission for S.Cr and outcome parameters like mortality, readmission and length of stay in hospital.

Statistical analysis

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using Independent T test /Mann Whitney test (when the data sets were not normally distributed) between two groups.Qualitative variables were correlated using Chi square test /Fisher exact test.Univariate logistic regression was used to find out association of various outcomes with AKI.A p value of <0.05 was considered statistically significant.

RESULTS

In present study, out of total 100 ADHF patients, 35 patients developed AKI during admission in hospital, where 68.81% (24/35) of patients were in stage 1 AKI followed by 22.73% (8/35) and 8.46% (3/35) of patients in stage 2 and 3. Change in serum creatinine from baseline values was observed among 88 patients where 86.43% (76/88) of patients had <=30 percent change in serum creatinine followed by 9.14% (8/88) and 4.43% (4/88) of patients had percentage change in serum creatinine levels of 31-60 and 61-100 respectively.

The mean age of the study population was 58.98 ± 17.16 years (Table 1). The mean age in AKI group was 62.03 ± 17.50 years while in non-AKI group it was 57.34 ± 16.88 years and the association between age and AKI was not significant (p=0.193). Age, weight, height and BMI had no statistically significant difference in the occurrence of AKI.For the AKI and non-AKI group, the mean duration of onset of symptom to admission was 4.54 ± 1.6 and 5.2 ±

1.58 hours respectively (p= 0.051). The occurrence of AKI was 62.86% and 37.14% in diabetic and non-diabetic patients respectively anddiabetes as a risk factor for the development of AKI was significant (p=0.029).Also, the occurrence of AKI among smokers and non- smokers was 57.14% and 42.86% respectively and this association was statistically significant (p=0.024).

Table 1.Baseline comparison among AFHD patients with or without AKI.

Baseline variables	No AKI (n=65)	AKI (n=35)	Total (n=100)	P value
	Number (%)/ Mean± SD			
Age (in years)	57.34 ± 16.88	62.03 ± 17.50	58.98 ± 17.16	0.193
Gender				
Female	32 (49.23%)	11 (31.43%)	43 (43.00%)	0.086
Male	33 (50.77%)	24 (68.57%)	57 (57.00%)	
Weight (Kg)	71.22 ± 11.86	75.74 ± 11.55	72.73 ± 11.88	0.082
Height (Cms)	164.98 ± 8.17	167.37 ± 7.48	165.82 ± 7.98	0.083
BMI (Kg/m^2)	26.19 ± 4.1	26.94 ± 3.51	26.45 ± 3.9	0.358
Duration from onset of symptomsto the admission (in hours)	5.20 ± 1.58	4.54 ± 1.60	4.97 ± 1.61	0.051
Comorbidity				
Diabetes	26 (40%)	22 (62.86%)	48 (48.00%)	0.029
Hypertension	28 (43.08%)	20 (57.14%)	48 (48.00%)	0.179
H/o smoking	22 (33.85%)	20(57.14%)	42 (42.00%)	0.024
H/o previous MI	21 (32.31%)	15 (42.86%)	36 (36.00%)	0.295
Peripheral Vascular Disease	11 (16.92%)	10 (28.57%)	21 (21.00%)	0.173
Hospital Stay	7.16± 4.39	8.47± 6.71	7.65± 5.22	0.242

The Boston Criteria was used to define ADHF. The Boston criteria of more than or equal to 8 was considered as ADHF. The mean Boston Criteria for the population was 9.87 ± 1.36. The means of the AKI and non-AKI group are 10.06 ± 1.3 and 9.77 ± 1.39. The p value of Student T test for Boston criteria and occurrence of AKI was 0.298 suggesting statistically insignificant relationship (Table 2).The most common aetiology of ADHF in the study population is ischemic heart disease (IHD), seen in 55% of the patients.

Table 2.Clinical presentation comparison among AFHD patients with or without AKI.

Clinical presentation	No AKI (n=65)	AKI (n=35)	Total (n=100)	P value
	Number (%)/ Mean± SD			
Symptoms and Signs				
Chest pain	38 (58.46%)	20 (57.14%)	58 (58.00%)	0.899
Rest Dyspnoea	31 (47.69%)	15 (42.86%)	46 (46.00%)	0.644
Orthopnoea	35 (53.85%)	12 (34.29%)	47 (47.00%)	0.062
PND	41 (63.08%)	23 (65.71%)	64 (64.00%)	0.793
Raised JVP	40 (61.53%)	17 (48.57%)	57 (57.00%)	0.211
Crackles	42 (64.64%)	25 (71.42%)	67 (67.00%)	0.489
Wheeze	19 (29.23%)	9 (25.71%)	28 (28.00%)	0.709
Third heart sound	23 (35.38%)	16 (45.71%)	39 (39.00%)	0.312
Boston Criteria	9.77 ± 1.39	10.06 ± 1.30	9.87 ± 1.36	0.298
Etiology of ADHF				

Ischaemia	32 (49.23%)	23 (65.71%)	55 (55.00%)	0.643
Valvular Lesion	14 (21.54%)	4 (11.43%)	18 (18.00%)	
Hypertension	10 (15.38%)	4 (11.43%)	14 (14.00%)	
Alcoholic Heart Disease	4 (6.15%)	1 (2.86%)	5 (5.00%)	
Restrictive Heart Disease	1 (1.54%)	1 (2.86%)	2 (2.00%)	
Other	4 (6.15%)	2 (5.71%)	6 (6.00%)	
Precipitating cause of ADHF				
Inadequate Medication	22 (33.85%)	6 (17.14%)	28 (28.00%)	0.407
Natural evolution	13 (20.00%)	7 (20.00%)	20 (20.00%)	
Ischaemic Event	15 (23.08%)	14 (40.00%)	29 (29.00%)	
Infection	7 (10.77%)	4 (11.43%)	11 (11.00%)	
Arrythmia	7 (10.77%)	4 (11.43%)	11 (11.00%)	
Other	1 (1.54%)	0 (0.00%)	1 (1.00%)	

The mean systolic blood pressure of the population was 122.78 ± 23.31 mm Hg. The mean SBP of the AKI and non-AKI group were 122.46 ± 20.51 mm Hg and 122.95 ± 24.84 mm Hg respectively. The association was statistically insignificant with p-value of 0.800.The mean serum creatinine concentration in AKI and non-AKI group were 1.73 ± 0.88 mg/dL and 1.13 ± 0.29 mg/dL respectively, whereas mean eGFR in the AKI and non-AKI group were 47.31± 23.22 mL/min and 69.70 ± 30.83 mL/min respectively and this association was statistically significant (p< 0.001).The prevalence of Diastolic dysfunction in the study population was 28.00%.

Table 3.Vital, laboratory and echocardiography parameters comparison among AFHD patients with or without AKI.

Parameters	**No AKI (n=65)**	**AKI (n=35)**	**Total (n=100)**	**P value**
	Number (%)/ Mean± SD			
Systolic BP(mm Hg)	122.95 ± 24.84	122.46 ± 20.51	122.78 ± 23.31	0.800
Diastolic BP(mm Hg)	73.28 ± 21.43	74.23 ± 21.43	73.61 ± 21.32	0.710
Hemoglobin(g/dL)	9.78 ± 1.45	9.67 ± 1.15	9.74 ± 1.35	0.772
Urea(mg/dL)	53.06 ± 14.05	60.29 ± 17.57	55.59 ± 15.68	0.038
Creatinine(mg/dL)	1.13 ± 0.29	1.73 ± 0.88	1.34 ± 0.63	<0.001
eGFR(mL/min)	69.79 ± 30.83	47.31±23.22	61.92 ±30.26	<0.001
Sodium (mmol/L)	137.11 ± 5.7	135.49 ± 5.02	136.54 ± 5.5	0.214
Potassium(mmol/L)	4.39 ± 0.56	4.52 ± 0.7	4.43 ± 0.61	0.617
SpO2	91.38 ± 4.46	91.23±3.87	91.33±4.24	0.627
EF	36.2±8.01	38.74±7.76	37.09±7.98	0.110
Diastolic Dysfunction on ECHO	13 (20.00%)	15 (42.86%)	28 (28.00%)	0.015

In present study prolonged hospital stay was the hospital stay length of 7 days or more than 7 days. Odds ratio for prolonged hospital stay with development of AKI as risk factor is 1.683.48 patients were readmitted after the index hospital admission.The odds ratio for readmission was 2.621. 12 patients died over the period of 3 months. Mortality was 8 in AKI group and 4 in the non-AKI group. The Odds Ratio for mortality was 4.519.

Table 4.Outcome among AFHD patients with or without AKI.

Outcome	No AKI (n=65)	AKI (n=35)	Total (n=100)	OR
	Number (%)			
Prolonged hospital stays	26 (42.62%)	15 (55.56%)	41 (46.59%)	1.683
Readmission	29 (47.54%)	19 (70.37%)	48 (54.55%)	2.621
Mortality	4 (6.15%)	8 (22.86%)	12 (12.00%)	4.519
Mortality in hospital or after discharge				
In Hospital Mortality	2 (50.00%)	5 (62.50%)	7 (58.33%)	1.667
Mortality after discharge (within 90 days)	2 (50.00%)	3 (37.50%)	5 (41.67%)	

DISCUSSION

In our study, occurrence of AKI was 35 out of 100 patients admitted with Acute Decompensated Heart Failure (35%). Several studies suggest the incidence in the range of 24-45%. This wide range is mainly attributable to the different definition used by different studies and heterogeneity of the population under study.[10,14,15]

The mechanism of action of WRF in patients of HF – cardiorenal syndrome are complex. It is due to decrease renal blood flow, elevated venous pressure, neurohormonal abnormalities such as excessive production of vasoconstrictive mediators (epinephrine, angiotensin and endothelin),and altered sensitivity to and/or release of endogenous vasodilatory factors (natriuretic peptide and nitric oxide).[16,17] During ADHF, AKI can be caused by both exacerbation of these mechanism and by low cardiac output. In comparison to the previous studies, we have excluded patients with cardiogenic shock and with eGFR < 60 ml/min. Higher incidence of AKI would have seen if cardiogenic shock and CKD stage IV and V were included, where it takes other mechanism that may have caused AKI.

Risk Factors for Development of AKI

The previous studies, concluded that the baseline S.Cr level,[3,10,14,15,18,19,20,21]hypertension,[3,14,21,22,23]diabetes mellitus,[3,22,23] pulmonary edema,[14,15]low hemoglobin, [19,22]low sodium,[24,25] overdiuresis,[23] low Ejection fraction,[21,22,23] were associated with AKI. According to our study, baseline KFT (B.Urea, S.Cr and eGFR),diabetes, past H/O smoking,diastolic dysfunction later found at Echo, were associated with AKI.

Baseline KFT showed stronger association with the incidence of AKI is suggestive of the fact that AKI is common in patients who have already impaired renal function. The nephron and overall kidney have a higher functional reserve in normal individual. Even a minimal increased baseline S.Cr, KFT, baseline B.Urea means already compromised renal function and highly reduced renal reserve. So, even a single insult like ADHF can be associated with AKI in the compromised renal reserve patients.

The most common association factor for development of AKI according to our study turned out to be Diabetes Mellitus. Around 50 % of study population was diabetic. The involved pathogenesis of renal injury is complex involving multiple mechanisms. It mainly involves, advanced glycation end product, glomerular hemodynamic factors,reactive oxygen species, upregulation of profibrotic growth factors and cytokines, and macrovascular complications involving atherosclerotic renal vessels. Diabetes Mellitus is also associated with AKI in patients with contrast nephropathy, analgesic renal injury, and other nephrotoxic agents.[24]

Diastolic Dysfunction is a condition in which filling of LV during diastolic is impaired, resulting in elevated filling pressures.Chittineni et al.,[20]and Logeart et al., [23] observed association between AKI and Diastolic Dysfunction. In about 50% 0f patients with CHF, Diastolic Dysfunction may be the probable cause of symptoms.Damman et al., [25]and Dries et

al., [26] found renal vein pressure in patients with ADHF. The altered pressure-volume relationship with diastolic dysfunction means that small volume changes may have an amplified effect on left ventricular filling and stroke volume.
In a study by Gambaro et al., it was noted that the renal plasma flow was reduced in chronic smokers compared to non-smokers and modest increase in plasma endothelin concentration. There is intense sympathetic excitation with increase in blood pressure (SBP upto 21 mm Hg), tachycardia and increase concentration of catecholamines in the circulation by smoking. It also causes increase in renovascular resistance of 11%.There is decrease in GFR by 15 % and Filtration fraction (-18%).[27]Our study found an association of impact of smoking on AKI induced by ADHF.

Outcomes

It was evaluated in terms of mortality; hospital stay and readmission. In various studies, comparing AKI in ADHF have found worse prognosis in patients with AKI compared to those without AKI. It has been reported that even a small deterioration in renal function has been associated with increased all-cause mortality in patients with chronic HF, independent of Age, LV systolic function and diabetes mellitus. [28]
We found the odds ratio of duration of hospital stay, readmission and mortality are 1.683, 2.621, and 4.519 respectively. All-cause mortality in different studies were1.91, 1.7, 7.5, 2.2, and 1.64 in Smith et al.,[29]Logeart at al.,[22]Foreman et al.,[3]De Silva et al.,[18]and Damman et al., [25]studies respectively.There was an increase in length of hospital stay of 2 days compared to 2.3 days, 2 days,and 3 days in Krumholz et at.,[14] Cowie et al.,[15]and Logeart et al.,[22]studies respectively.

Limitations

The sample size is small for detection of risk factors that had a subtle impact on the outcomes. Our study did not take into account the effect of medications and interventions during the admission period of the study population. Effect of diuretics and ACE inhibitors need to be considered as risk factors for the development of AKI in ADHF. Our study did not evaluate the use of novel biomarkers NGAL, Cystatin C for detection of AKI. Being an observational study, we could not evaluate various management protocols for management of ADHF to prevent AKI.

CONCLUSION

Cardio-renal syndrome is a commonly seen in patients admitted in hospital. AKI can lead to poor cardiac output or pre-renal failure as a result of overuse of diuretics. The mechanism involved is complex. AKI in patients admitted with ADHF has poor prognosis with increased mortality and longer duration of hospital stay. Treatment for heart failure has proven efficacy and survival benefits. Significant predictors of renal dysfunction include raised baseline serum creatinine, smoking and presence of diastolic dysfunction and history of diabetes. Early diagnosis of AKI is important to take therapeutic measures to prevent worsening of renal functions novel biomarkers play an important role, and more research is required in this field.

REFERENCES

1. McMurray JJV, Pfeffer MA. Heart failure. Lancet. 2005;365:1877-89.
2. Ronco C, Haapio M, House AA, Anavekar N, Belllomo R. Cardiorenal Syndrome. J Am CollCardiol. 2008;52(19):1527-39.

3. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS,et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am CollCardiol 2004;43:61-7.
4. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, et al. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. Kidney Int 2004;66:1613-21.
5. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. J Am Soc Nephrol 2004;15:1597-605.
6. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol 2010;21:345-52.
7. Amin AP, Salisbury AC, McCullough PA, Gosch K, Spertus JA, Venkitachalam L, et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. Arch Intern Med 2012;172:246-53.
8. Marenzi G, Cabiati A, Bertoli SV, Assanelli E, Marana I, De Metrio M, et al.Incidence and relevance of acute kidney injury in patients hospitalized with acute coronary syndromes. Am J Cardiol 2013;111:816-22.
9. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:8-12.
10. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 2002;8;136-41.
11. Susan MJ, Cedars AM, Ewald GA, Geltman EM, Mann DL. Acute decompensated heart failure. Tex Heart Inst J 2009;36(6):510-20.
12. Shamsham F, Mitchell J. Essentials of the diagnosis of heart failure. Am Fam Physician 2000;61(5):1319-28.
13. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy and heart failure outcomes: evidence from the digoxin intervention group trial. J Am Soc Nephrol 2004;15(8):2195-203
14. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Redford Ml, Bradford WD et al. Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure. Am J Cardiol 2000;85:1110-3.
15. Cowie MR, Komajda M, Murray Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective study in heart failure (POSH). Eur Heart J 2006;27:1216-22.
16. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Chalesworth A et al. Renal function, neurohormonal activation and survival in patients with chronic heart failure. Circulation 2000;102(2):203-10.
17. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A sub study of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724-9.
18. De Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J 2006;27:569-81.
19. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM et al. Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. J Card Fail 2006;12:257-62.

20. Chittineni H, Miyawaki N, Gulipelli S, Fishbane S. Risk for acute renal failure in patients hospitalized for decompensated congestive heart failure. Am J Nephrol 2007;27:55-62.
21. Zhou Q, Zhao C, Xie D, Xu D, Bin J, Chen P et al. Acute and acute-on-chronic kidney injury of patients with decompensatcd heart failure: impact on outcomes. BMC Nephrol 2012;13:51-60.
22. Logeart D, Tabet JY, Hittinger L, Thabut G, Jourdain P, Maison P et al. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. Int J Cardiol 2008;127:228-32.
23. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am CollCardiol 2008;51:1268-74.
24. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM et al. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 1986;77:1925-30.
25. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, et al. Worsening renal function and prognosis in heart failure: Systemic review and meta-analysis. J Cardiac Fail 2007;13:599-608.
26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am CollCardiol 2000;35:681-9.
27. Gambaro G, Verlato F, Budakovic A, Casara D, Saladini G, Del Prete D et al. Renal impairment in chronic cigarette smokers. J Am Soc Nephrol 1998;9:562-7.
28. The SOLVD Investigators: Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. N Engl J Med 1992;327(10):685-91.
29. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure. J Card Fail2003;9:13-25.