RESEARCH ARTICLE

Frequency, predictors and prognosis of worsening renal function in patients admitted with acute heart failure

Vinod Kumar, Saba Aijaz, Sadia Sattar, Asad Pathan

Abstract

Objective: To calculate frequency of worsening renal failure (WRF) in patients with acute decompensated heart failure (ADHF), to evaluate predictors of WRF and to assess its effect on in-hospital and 12 month adverse outcomes.

Methods: A single center observational prospective study was conducted on consecutive patients admitted with ADHF from Sept 2016 - February 2017. Follow-up was done for 12 months post discharge. Data were obtained from electronic medical records and telephonic calls. Early adverse outcome was composite of hospital mortality, prolonged length of stay (LOS) >4days or new need for haemodialysis. Intermediate term adverse event was composite of 12 months all-cause mortality or re-hospitalization.

Results: Total of 247 ADHF patients were admitted. Mean age was 67.6±33.4 years. Males were 163 (65.9%). WRF was found in 57 (23.1%) patients. Predictors of WRF were age>70years, furosemide dose>400mg and admission eGFR <60ml/min. The odds of composite in-hospital outcomes were four times higher in WRF compared to stable renal function (38.6% versus 13.2%, (p<0.01) but were mainly driven by prolonged LOS (4.2 vs. 2.2 days respectively). Follow up was available for 230(97%). Intermediate term outcome was not different between two groups on log rank test.

Conclusion: WRF is a significant problem in ADHF, is common in elderly patients, with baseline impaired renal function and is associated with high requirement of diuretics and prolonged hospital stay. Composite of mortality or HF hospitalization at 12 months was not different between the two groups.

Keywords: Worsening renal function, decompensated heart failure, chronic kidney disease.
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Introduction

Acute decompensated heart failure (ADHF) is a frequent cause of hospitalization for patients with heart disease and this may be associated with reduced or preserved left ventricular systolic function.[1] Patients with ADHF are at high risk of readmission- up to 30% at three months[2] and have worse short and long term survivals with mortality as high as 46% at one year.[3] A small study based on Pakistani patients with underlying systolic heart failure (HF) showed readmission rate of 37.2% and overall mortality of 27.5% at one year after ADHF hospitalization.[4]

Some patients with ADHF have deterioration in their renal function during hospitalization and this worsening renal failure (WRF) is an adverse prognostic factor among such patients.[5,6] In a recent meta-analysis WRF developed in 23% patients admitted with ADHF. These patients had 1.62 times higher odds of dying at six months,[7] along with increased length of stay and readmission rates.[8] Small studies have suggested that predictors of developing WRF are baseline impaired renal function, low LV ejection fraction and older age.[6,9]

There is paucity of data from South Asia reporting on ADHF or prevalence and prognosis of WRF. South Asians with heart failure tend to have lower Ejection Fraction (EF), higher readmission and less mortality compared to Caucasians.[10] Thus the main objectives of this study were to calculate the frequency of WRF in patients admitted with ADHF, to explore the predictors of WRF and to assess its effect on in-hospital and 12 months adverse outcomes.

Methods

This was an observational prospective cohort study conducted in Tabba Heart Institute Karachi on patients

Tabba Heart Institute, Karachi, Pakistan.
Correspondence: Asad Pathan. e-mail: asadzpathan@gmail.com

admitted between Sept 2016 and February 2017with clinical diagnosis of ADHF and requiring diuretics (ICD code 10). Worsening renal function was defined as a decrease of 25% in eGFR(estimated glomerular filtration rate) from baseline value.[7] eGFR was calculated at baseline and with maximum creatinine using MDRD equation.[11] Abnormal renal function was defined as eGFR of <60 ml/m2. Records from patients file and hospital's electronic medical record software was extracted on key demographic, clinical parameters, serum creatinine, LV ejection fraction (EF), dose of intravenous or oral furosemide utilized, plasma BNP (brain natriuretic peptide) levels, length of hospital stay and vital status. Patients were also followed up for12 months after index hospitalization to record survival and need for readmission for heart failure (HF). Follow up was completed; wherever missing; using telephone calls. Ethical Review Committee approval was sought prior to start of the enrollment. Patients with heart failure secondary to cardiac tamponade, aortic dissection, acute coronary syndrome or arrhythmias, those undergoing contrast-enhancing imaging and on chronic haemodialysis were excluded.

Primary outcome was incidence of WRF and secondary outcome was to explore predictors of WRF. Another secondary outcome was early and intermediate term prognosis. Early adverse outcome was defined as composite of hospital mortality, prolonged length of stay (more than 4 days) or new need for haemodialysis after 24 hours of admission. Intermediate term adverse event was composite of12 months all-cause mortality or need for HF hospitalization after discharge.

With a reported incidence of WRF at 25%, as shown by Damman et al,[7] and a degree of freedom of 0.06, and alpha of 5%, the estimated sample size for primary outcome was minimum 201 patients.

SPSS version 21 was used for statistical analysis. For continuous variables, means and standard deviation were estimated and for categorical variables, percentages and frequency werecalculated. For analysis of continuous variables, students t-test or Mann Whitney U test was used depending upon whether distribution of the variable was normal while for categorical variable chi-square test was used. Frequency of WRF was reported as percentage. Predictors of WRF were assessed through multivariate logistic regression analysis using clinically significant variables derived from prior studies as well as those that were significant on univariate analysis.

Prognostic early adverse outcomes were compared between the WRF and stable renal function groups using odds ratio and 95% confidence intervals. For intermediate term outcome comparison, hazard ratio and 95% confidence interval was reported. Survival was graphically displayed using Kaplan-Meier curves. Median time to event was reported. Log rank p-value <0.05 was taken as significant.

Results

During the study period247 patients were admitted with ADHF. Mean age was 67.6 ± 33.4years. Majority163 (65.9%) were males. Mean serum creatinine was 1.58 ± 0.89 mg/dl and 86 (34.8%) patients had abnormal renal function at baseline. A total of 216 (87.4%) patients had HF with reduced EF (HFrEF) i.e. EF ? 40%. BNP levels were available for 200 (80.9%) patients with median levels of 1125 (IQR: 600-2501). Median dose of Furosemide was 400 mg (IQR: 240-660). Median length of stay was two days (IQR: 1-4). Haemodialysis was required in 11 (4.5%) and 09 (3.6%) patients died during hospitalization.

Out of 247 admitted HF patients, 57 (23.1%) had worsening renal failure during hospital stay. Difference in baseline eGFR level between the two groups (60.2 ± 23.7 ml/min

Table-1: Comparison of major baseline variables in patients admitted with heart failure, with and without worsening renal function (n=247).

Parameters	Overall n= 247	Worsening renal function n=57 (23.1%)	Stable renal function n=190 (66.9%)	*p*-value
Age (years)	65.67 ±12.01	68.51 ± 11.51	64.82 ± 12.10	0.05
Males	163 (65.9)	36 (63.1)	127 (66.8)	0.5
Hypertension	196 (79.3)	47 (82.4)	149 (78.4)	0.48
Diabetes mellitus	150 (60.7)	40 (70.1)	110 (57.9)	0.31
Atrial fibrillation	43 (17.4)	10 (16.7)	33 (17.3)	0.42
HF with reduced EF (HFrEF)	223 (91.0)	50 (87.7)	173 (92.0)	0.35
Admission systolic BP (mmHg)	135.77 ± 29.38	142.79 ± 29.38	133.66 ± 29.12	0.07
Need for inotropes	23 (9.3)	5 (8.8)	18 (9.5)	0.28
Baseline Haemoglobin < 10gm/dl	32 (12.9)	7 (11.7)	25 (13.1)	0.24
Furosemide dose, mg (Median/IQR)#	400 (420)	610 (760)	360 (360)	0.0003$
Baseline eGFR (MDRD)	54.94 ± 25.22	53.15 ± 25.38	60.91± 23.97	0.04
Baseline eGFR< 60 ml/min	145 (58.7)	36 (63.2)	84 (43.6)	0.01
Minimum eGFR (MDRD)	47.77 ± 22.58	37.91± 17.60	50.64± 23.16	0.002
Length of stay (days)	2 (3)	4.2 (4)	2.2 (2)	0.0001$

Values are frequency and percentages for categorical variables and means and standard deviation for quantitative variables, Student's t-test was utilized (unless specifically mentioned) for continuous variables and chi-square for categorical variables.# IQR: Inter quartile range is provided within brackets with median doses, $ Mann Whitney U test.

Table-2: Predictors of worsening renal function in multivariable regression analysis.

Parameter	Adjusted Odds Ratio	95% Confidence interval	p-value
Age > 70 years	2.7	1.4 - 5.4	0.005
Baseline eGFR < 60 ml/min	3.2	1.4 - 7.1	0.005
Furosemide dose> 400mg	5.2	2.5 - 10.7	<0.001

*Other variables entered for regression analysis but found insignificant were: Presence of DM, Prior known chronic kidney disease, systolic BP <90 at presentation, need of inotropes and presence of HFrEF.

Table-3: Medication prescription pattern in patients admitted with heart failure, with and without worsening renal function.

	Overall patient population	Worsening renal functiong group	Stable renal function group
Medications at admission (n=213)			
ACE-I/ARBs	117 (54.9)	21/43	96/170
Beta blockers	167 (78.0)	32/44	165/170
Aldosterone antagonists	59 (27.8)	6/43	53/169
Diuretics	149 (70.3)	28/43	121/169
Hydralazine + Nitrate	35 (16.5)	7/43	28/169
NSAIDs	5 (2.4)	1/43	4/169
Ivabradine	16 (7.3)	3/46	13/173
Medications during hospitalization (n=247)			
ACE-I/ARBs	148 (59.9)	37/57	111/190
Aldosterone antagonists	99 (40.1)	24/57	75/190
Discharge medications (Alive=238)			
GDMT (BB with ACE-I/ARB / HDZ+Nitrates)	193 (81.8)	44/54	149/181
ACE-I/ARBs	134 (57.0)	27/54	107/181
Beta blockers	207 (88.1)	48/54	159/181
Aldosterone antagonists	115 (48.9)	22/54	93/181
Diuretics	225 (95.7)	49/54	174/181
Hydralazine + Nitrate	69 (29.4)	18/54	51/181
Ivabradine	24 (10.2)	6/54	18/181

Abbreviations: ACE-I indicates angiotensin-converting enzyme inhibitor; ARBs, angiotensin-II receptor blockers; BB, beta-blockers; GDMT, guideline-directed medical therapy; HDZ, hydralazine; NSAIDs, non-steroidal anti-inflammatory drugs.

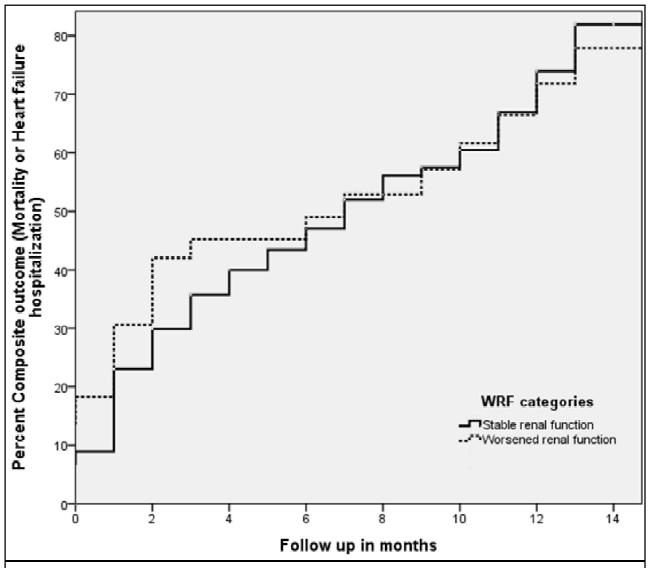

Figure: Comparison of composite 12months outcome among renal function categories. (p-value: 0.88).

in stable renal function versus 53.1 ± 25.3 ml/min in WRF) was statistically significant. There was borderline difference between age of patient with and without WRF. However there was no difference between the groups in other baseline parameters including presence of Diabetes Mellitus, Hypertension, prior chronic kidney disease, HFrEF, systolic Blood Pressure on admission or need for inotropic support. Also there was significant difference between amount of median furosemide dose between the WRF and stable RF patients (610 versus 360 mg). Logistic regression model indicated age> 70 years, furosemide dose> 400 mg and admission eGFR < 60 ml/min as significant predictors of WRF. (Table 2)

The details on different heart failure medicines utilization during hospital stay are provided in table 3. There was no statistically significant difference in individual medications use among the two groups except that Aldosterone antagonists were underutilized in WRF group compared to stable RF (14.0 vs. 27.8, p-value: 0.02). Around 80% were discharged on at least 3 GDMT medicines (including a beta blocker and either ACE-I/ARB or Hydralazine + Nitrate combination or Aldosterone antagonists) with no significant difference between the two groups. Also there was no difference in individual discharge medications.

The odds of composite in hospital outcomes

Table-4: Comparison of primary and secondary outcomes and their components in heart failure patients with and without worsening renal function during hospitalization.

	Overall	Worsening renal function	Stable renal function	OR (95%CI)	P-value
Adverse outcomes during hospitalization(n=247)					
Overall	47 (19.0)	22 (38.6)	25 (13.1)	4.1 (2.1-8.2)	<0.0001
Length of Stay > 4 days	36 (15.1)	19 (33.3)	17 (9.4)	5.0 (2.4 - 10.7)	0.00002
Need for haemodialysis	11 (4.5)	5 (8.8)	6 (3.2)	2.9(0.8 - 10.0)	0.1
Mortality	9 (3.6)	2 (3.5)	7 (3.7)	0.9 (0.19 - 4.7)	0.5
12 months after discharge(n=230)					
Overall	138 (60.0)	34(63.0)	104 (59.1)	1.08 (0.7 - 1.6)#	0.4
All-cause mortality	26 (11.3)	5 (9.3)	21 (11.9)	0.8 (0.3 - 2.0)#	0.6
HF-hospitalization	112 (48.7)	29 (53.7)	83 (47.2)	1.1 (0.7 - 1.7)#	0.4

#: Hazard Ratio.

were four times higher in WRF group compared to stable renal function (38.6% versus 13.2%, (p <0.01). However on analysis of the individual components this difference was mostly driven by prolonged hospital stay in the WRF group. Odds ratios and p-values are shown in table 4.

Follow up was available for 230 out of 237discharged patients (97%). Median follow up duration was 10 months (IQR: 3 - 14). There were 26 (11.3%) deaths. Need for HF hospitalization was required in 112 (48.7%). More than a quarter of repeat hospitalizations occurred within 30 days of index admission and approximately 70% repeat hospitalizations were within 90 days of index admission. Composite of mortality or HF hospitalization at 12 months was not different between the two groups on log rank test. Hazards ratios with p-values are given in table 4, Kaplan Meier curve can be seen in figure.

Discussion

In our study, out of 247 total patients admitted with ADHF, incidence of WRF was 23%. Statistically significant independent predictors included age> 70 years, baseline eGFR less than 60ml/min and total furosemide dose> 400 mg. WRF subgroup had longer hospital stay compared to no WRF while need for haemodialysis and hospital mortality were similar. Also there was no difference in mortality or HF re-hospitalization rates at follow up duration of 12 months however overall half of the patients were readmitted with heart failure during the follow up period.

The incidence of WRF is variable among current literature due to difference in the definition used and is around 25% as shown in a meta-analysis by Damman et al,[7] our result being consistent with these findings. WRF incidence is unaffected by HFpEF or HFrEF status however due to small proportion of HFpEF patients in our study, definitive conclusion cannot be generated in this regard.[12] Various mechanisms postulated for development of WRF in acute HF include venous congestion, low cardiac output and renal hypoperfusion, and on the other hand aggressive diuresis and haemo-concentration.[13-15] Multiple studies have shown various predictors of WRF in ADHF patients including age, diabetes mellitus, hypertension, NYHA class at presentation, presence of chronic kidney disease at baseline and high dose diuretic use.[5,16,17] In our study baseline eGFR and age are significant independent predictors of WRF which is consistent with the literature.

Our study has shown significant association of higher requirement of furosemide in WRF patients, similar to few other small studies. Although there is no clear mechanism for this association of increased prevalence of WRF and higher diuretics dose but literature has shown that diuretics may cause direct adverse effect on eGFR.[18] Diuretics are mainstay of therapy in HF as they reduce LV filling pressures by acting as systemic venodilators and remove excess volume through the kidneys. Diuretic dose is not predetermined and is titrated according to patient's clinical response and urine output. In addition to invasive pulmonary wedge pressure monitoring, there are certain noninvasive modalities such as echocardiographic assessment of LV filling pressures and lung ultrasound for pulmonary congestion that can help in judicious utilization of diuretics; these remain mostly under used in clinical settings.[19,20] High dose diuretics can trigger activation of counter regulatory mechanism of renal vasoconstriction thus reducing GFR and resulting in acute renal dysfunction.[21] Requirements of higher doses of furosemide may also be related to resistant or severe HF where renal perfusion is itself compromised and there may not be adequate urine output with modest diuretic doses.[22] Thus high diuretics dose may both be a cause and a consequence of WRF in severe HF. [23]

The overall readmission rate in HF patients was 48% in our study which is consistent with current international data.[24] Although there was no statistical difference in readmission rates between WRF and no WRF; slightly higher readmission rates were observed in WRF. Recurrent hospitalization contribute to overall decline in HF prognosis and increased mortality.[25] Interventions like implantable monitors to assess filling pressures have shown promising results in terms of reduced rehospitalization rates. Other rather cost effective methods include use of telemedicine with monitoring of patient's symptoms, weight and haemodynamics and use of nurse practitioners and integrated care leading to systematic management.[26-28]

According to our results, longer hospital stayin patients with WRF is the main contributing factor towards initial adverse outcomes which is twice of those with no WRF. Association of WRF in ADHF with prolonged hospital stay is a recognized factor.[17] Length of stay is directly related to cost of treatment A study by Krumholz et al. have shown that in hospitalized ADHF patients, for an increase length of stay of 2.3 days due to WRF, the cost increases at least 30% compared to no WRF.[29] Although cost analysis was

not our primary objective; the magnitude of impact on cost related to length of stay may be different from Western data.

Multiple studies have shown association between persistent or transient WRF and poor out of hospital prognosis in terms of mortality and readmission with HF regardless of LVEF.[30-32] Our study failed to show the long term prognostic difference between the two groups despite vigorous follow up. Prime explanation could be that our study was not adequately powered to show prognostic difference and studies of larger sample size and longer follow ups can clarify on the prognosis in our population. Differences in rehospitalization may be secondary to difference in treatment prescriptions between two groups as the patients with WRF had either not been suggested/prescribed RAAS inhibitors or given lower doses as compared to patients with stable or normal renal function.

Although this is the first research from Pakistan reporting on this topic, the chief limitation of our study is being a single center study with a short follow up period.

Conclusion

WRF arises in a considerable proportion of patients admitted with heart failure, is common in elderly patients with baseline impaired renal function and is associated with high dose diuretics use. WRF has significant effect on length of hospitalization and thus has a reasonable economic impact. However to assess long term effects of WRF in ADHF, larger sized studies are needed.

In future, there is need to develop economic preventive and treatment strategies for WRF and utilization of noninvasive diagnostic tools to guide diuretic therapy in HF patients.

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