



Worsening Renal Function in Acute Decompensated Systolic Heart Failure; Observations from RASHF Registry, an Iranian Heart Failure Registry

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ABSTRACT

Background: Heart Failure (HF) is a major cause of morbidity and mortality worldwide. Additionally, Worsening Renal Function (WRF) during hospitalization has a significant effect on re-hospitalization and mortality in such patients.

Objectives: The present study aimed to determine the prevalence and prognostic significance of WRF complicating acute HF in patients enrolled into Rajaie Acute Systolic Heart Failure (RASHF) registry.

Patients and Methods: RASHF registry is a single-center, prospective, observational, hospital-based study of systolic HF patients with Left Ventricular Ejection Fraction (LVEF) \leq 35% admitted with acute decompensation. The patients were enrolled for 10 months from March 2012 to February 2013. The primary endpoint of the study was WRF. In addition, the secondary endpoints were in-hospital mortality and death within 3 months after discharge.

Results: This study was performed on 230 patients (82% male). About one thirds of the patients (29.1%) developed WRF. Although some characteristics of the patients with WRF, including etiology of HF, NYHA functional class, and presence of risk factors, were similar to those of other patients, they were older, had more congestive symptoms, and had higher baseline creatinine levels. The incidence of in-hospital mortality was 9.6%. Length of hospital stay (14 days versus 8 days, $P < 0.001$), in-hospital mortality (23.9% versus 4.9%, $P < 0.001$), and death during 3 months after discharge (19.4% versus 13.4%, $P < 0.001$) were higher among the patients with WRF.

Conclusions: WRF was quite common in the patients with Acute Heart Failure (AHF) and was associated with higher in-hospital mortality and decrease in early survival after discharge.

► Implication for health policy/practice/research/medical education:

This study was the report of a hospital-based registry for acute heart failure in which, the incidence of WRF during hospital stay and its predictors and mortality rate were evaluated for the first time in an Iranian heart failure registry.

1. Background

Today, despite advances in management of chronic heart failure, there are many unsolved problems in the area of Acute Heart Failure (AHF). The majority of evidences in this issue are from large registries and the treatment

approaches retrieved from experts' opinions in most centers (1). Because of the increase in the incidence of AHF and its related mortality and morbidity, many registries have been designed throughout the world for better description of the clinical characteristics, complications, and outcomes of these patients (1).

One of the most important issues in AHF area is Worsening Renal Function (WRF) defined as an absolute increase in

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serum Creatinine (Cr) \geq 0.3 mg/dL from baseline during management of acute decompensated heart failure. WRF can occur in up to one thirds of patients admitted for AHF and its prognostic significance has been well described. WRF was associated with increased risk of short- and long-term mortality as well as prolonged hospital stay and increased readmissions (2-6). Despite many investigations conducted in this area, little is known about the precise mechanism of WRF. Indeed, investigators of the majority of these studies have come to very conflicting results regarding the causal association between WRF and other findings, such as patients' characteristics, laboratory and hemodynamic parameters, and treatment modalities (2-6).

Generally, ethical issues may prohibit designing of randomized clinical trials for many aspects in the setting of AHF. Therefore, many experiences in management of AHF have come from clinical data registries. In clinical data registries, many outcome measures of study populations can be identified after data collection.

Rajaie Acute Systolic Heart Failure (RASHF) registry is the first Iranian AHF registry from a tertiary center for cardiovascular medicine running advanced heart failure programs in Tehran, Iran.

2. Objectives

The present study aims to investigate WRF in AHF and describe the prevalence and prognostic significance of WRF complicating AHF in patients enrolled in the RASHF registry.

3. Patients and Methods

RASHF registry is a single-center, prospective, observational, hospital-based study of systolic heart failure patients admitted with acute decompensation in Rajaie Cardiovascular Medical and Research Center, a tertiary center for advanced heart failure and transplantation programs in Tehran, Iran.

In the current study, the patients were enrolled for 10 months from March 2012 to February 2013. The inclusion criteria for registration were aging above 18 years, having the signs and symptoms of new-onset or worsening heart failure according to accepted guidelines (7), and Left Ventricular Ejection Fraction (LVEF) \leq 35%. On the other hand, patients with acute coronary syndrome and cardiogenic shock and end-stage renal disease patients on chronic hemodialysis were excluded from the study.

The study data were collected on admission and throughout the hospital course by the expert registry team. All the patients were subsequently followed for 3 months for re-hospitalization or death. During admission, a comprehensive medical and drug history was taken and thorough physical examination and echocardiography were performed by an expert cardiologist. Moreover, the laboratory data, including Complete Blood Count (CBC), blood sugar, Blood Urea Nitrogen (BUN), serum Cr, sodium (Na), potassium (K), and magnesium (Mg), liver enzymes, and bilirubin, were recorded on admission. BUN and Cr levels were recorded on a daily basis until the discharge day. All laboratory tests were performed in the clinical laboratory of Rajaie Cardiovascular Medical and Research

Center using routine standard laboratory methods. Then, the data were recorded in the software designed by the medical Information Technology (IT) team of Rajaie Cardiovascular Medical and Research Center. The recorded data were controlled by trained nurses and an expert cardiologist every day.

This study was approved by the Institutional Research and Ethics Committee of Rajaie Cardiovascular Medical and Research Center. In addition, written informed consents for taking part in the study were obtained from all the participants.

3.1. Definitions

3.1.1. Acute Decompensated Heart Failure

Acute decompensated heart failure was defined as rapid and/or sudden onset or worsening of the symptoms and signs of heart failure caused by severe congestion and fluid overload in multiple organs or in adequate cardiac output, which required immediate evaluation and treatment (7).

3.1.2. Worsening Renal Function (WRF)

WRF was defined as an absolute increase in serum Cr \geq 0.3 mg/dL from baseline in at least two consecutive samples during the index hospitalization up to discharge (2-6).

3.1.3. Patients' Symptoms and Signs

The New York Heart Association (NYHA) function class was determined by evaluating each patient at rest and during different activities, including dressing, walking, and climbing the stairs. The scores given to each patient ranged from I (no symptoms) to IV (symptoms at rest) (7).

Edema was determined to be severe if it was estimated as 4+ according to the following grading system (8):

- 1+: Slight pitting, no visible distortion, disappears rapidly,
- 2+: Somewhat deeper pit, no readably detectable distortion, disappears in 10 - 15 seconds (2 - 4 mm indent),
- 3+: Pit is noticeably deep, may last for more than 1 minute, dependent extremity looks fuller and swollen (4 - 6mm), and
- 4+: Pit is very deep, lasts for as long as 2 - 5 minutes, dependent extremity is grossly distorted (6 - 8 mm).

3.1.4. Patients' Findings in Medical History

Ischemic Cardiomyopathy (CMP) was defined in case of having the history of acute myocardial infarction associated with wall motion abnormalities and/or ischemic scar tissues in non-invasive imaging studies (echocardiography, cardiac magnetic resonance imaging, and nuclear myocardial perfusion imaging) or significant coronary artery disease in at least one epicardial coronary artery.

Non-ischemic CMP was defined as structural and functional myocardial abnormality in the absence of coronary artery disease, which might be idiopathic or secondary to hypertension, valvular heart disease, neurological disorders, etc.

Diabetes mellitus was determined by having the history of diabetes mellitus and/or treatment with hypoglycemic agents or insulin, fasting blood sugar $>$ 126 mg/dL, or HbA1c $>$ 6.5 %.

Hypertension was determined by having a positive history of hypertension and/or its treatment based on approved recommendations. Hyperlipidemia was defined as the positive history of dyslipidemia and/or its treatment based on approved recommendations.

Smoking was determined by the positive history of smoking cigarette or water pipe. Chronic kidney disease was defined as Cr > 1.5 mg/dL for at least 3 months before admission.

3.2. Study Endpoints

The primary endpoint of the study was the occurrence of WRF during the hospitalization course. In addition, the secondary endpoints were in-hospital mortality and re-hospitalization or death within 3 months after discharge.

3.3. Statistical Analysis

All statistical analyses were performed using the SPSS statistical software for windows, version 19 (IBM Corp, Armonk, NY, US). At first, Kolmogorov-Smirnov test was used to assess the normal distribution of the data. Continuous variables were presented as mean (Standard Deviation, SD) or median (Inter Quartile Range, IQR) as appropriated. The categorical data were also presented as numbers (percentages). Continuous variables were compared using Student's t-test or Mann-Whitney U test, while categorical ones were compared through chi-square test.

Predictors of WRF, in-hospital mortality, and mortality within 3 months were first assayed by univariate analysis. Then, binary multivariate regression analysis was used to

define the independent predictors. Finally, the three-month survival was determined using Kaplan-Meier method. $P < 0.05$ was considered to be statistically significant.

4. Results

During 10 months from March 2012 to February 2013, a total of 230 patients (82% male) were enrolled into this study. The mean (SD) age of the patients was 53 (16) years.

Regarding the etiology of heart failure, 113 (49%) and 117 (51%) study participants had ischemic and non-ischemic CMP, respectively. Besides, 9 patients (4%) were admitted with the diagnosis of acute denovo heart failure and the rest as acute decompensated heart failure. The most common cause of decompensation was non-compliance with drugs (34%) or diet (33%). Among the patients with non-ischemic CMP, 88 had idiopathic dilated CMP, 11 valvular CMP, 2 chemotherapy induced CMP, 3 familial CMP, 2 CMP secondary to drug abuse, 1 peripartum CMP, 2 restrictive CMP with reduced LVEF, 3 hypertensive CMP, 2 hemochromatosis, 1 Fredrich ataxia, 1 alcoholic CMP, and 1 CMP secondary to connective tissue diseases. The participants' demographic and clinical characteristics have been presented in Table 1. Besides, the participants' medical treatments during the hospital course have been depicted in Table 2. As shown in Table 2, most of

Table 1. Demographic, Clinical, and Laboratory Findings of the Study Population (n = 230)

Characteristics/Variables Count (%)	Total, n = 230	Non-WRF, n = 163	WRF, n = 67	P value
Age (mean, years)	53(16)	51.5(16.6)	59.6(16.4)	0.02
Gender				
Female	42(18)	29(17.8)	13(19.4)	0.7
Male	188(82)	134(82.2)	54(80.6)	
Etiology				
Ischemic cardiomyopathy	113(49)	77(47.2)	36(53.7)	0.3
Non-ischemic cardiomyopathy	117(51)	86(52.8)	31(46.3)	
Diabetes, number (%)	77(34)	55(33.7)	22(32.8)	0.9
Hypertension, number (%)	55(24)	36(22.1)	19(28.4)	0.3
Smoking, number (%)	75(33)	59(36.2)	16(24)	0.07
Previous MI, number (%)	52(23)	39(24)	13(19.4)	0.4
ICD /CRT (%)	37(16)	27(16.5)	10(15)	0.5
NYHA class, number (%)				
I	3(1)	3(1.8)		0.3
II	48(20)	37(22.7)	11(16.4)	
III	140(60)	96(59)	44(65.7)	
IV	39(17)	27(16.6)	12(17.9)	
Severe peripheral edema, number (%)	53(23)	23(17)	30(33)	0.004
Elevated JVP, number (%)	199(87)	139(85.3)	60(89.6)	0.3
Ascites, number (%)	59(26)	31(19.3)	28(41.8)	< 0.001
Systolic BP, mm/Hg (median, IQR)	110(100 - 120)	100(100 - 120)	110(91 - 120)	0.64
Diastolic BP, mm/Hg (median, IQR)	70(60 - 80)	70(60 - 80)	70(60 - 80)	0.35
Heart rate (median, IQR)	84(70 - 100)	84(70 - 100)	80(70 - 100)	0.17
Baseline creatinine, mg/dL (median, IQR)	1.2(1 - 1.5)	1.1(0.9 - 1.3)	1.4(1 - 1.9)	0.005
Discharge creatinine, mg/dL (median, IQR)	1.1(0.9 - 1.5)	1(0.9 - 1.2)	1.9(1.3 - 2.8)	< 0.001
First creatinine > 1.5 mg/dL, Number (%)	43(19)	18(13)	25(28)	0.006
LVEF (median, IQR)	20(15 - 23)	17(15 - 20)	20(15 - 25)	0.7
Length of hospital stay, days (median, IQR)				
stay, days (median, IQR)	9(6 - 15)	8(5 - 12)	14(8 - 22)	< 0.001
In-hospital mortality (%)	22(9.6)	8(4.9)	16(23.9)	< 0.001
Death during 3 months after discharge (%)	35(15.2)	22(13.5)	13(19.4)	< 0.001
Rehospitalization rate during 3 months	69(30)	45(28)	23(34)	0.41

Abbreviations: BP, blood pressure; CRT, cardiac resynchronization therapy; ICD, intra-cardiac defibrillator; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, New York heart association; WRF, worsening renal function

Table 2. History of Medications Consumed by the Study Population (n = 230)

Drugs	Total, n = 230	WRF, n = 67	Non-WRF	P value
Beta blockers, %	83	78	90	0.23
ACEI or ARB, %	85	84	86	0.23
Spirolactone, %	72	78	63	0.21
IV Furosemide, %	88	90	89	0.72
Metolazone, %	20	9	6	0.62
Digoxin, %	34	33	36	0.89
Warfarin, %	23	27	18	0.06
Atorvastatin, %	38	36	40	0.43
Amiodarone, %	13	12	13	0.8
Aspirin or clopidogrel, %	40	42	35	0.42
Hydralazine, %	20	15	27	0.36

the patients were receiving guideline recommended medical treatments.

Furosemide is the only available loop diuretic in our center. Intravenous (IV) furosemide was started for almost 90% of the patients on admission. Additionally, 11% and 22% of the patients needed IV vasodilators and inotrope, respectively during their admission course.

Heart failure symptoms on presentation have been shown in Table 1. Although the patients with cardiogenic shock were excluded from this study, Systolic Blood Pressure (SBP) was less than 90 mmHg in 22 patients (9.5%) on admission. Moreover, dyspnea was the most common symptom of heart failure (98%) and most of the patients were in NYHA class III (60%). The frequency of the symptoms and signs of heart failure in our study population has been presented in Figure 1 and Figure 2.

4.1. Worsening Renal Function (WRF)

During the hospital course, 67 patients (29.1%) patients developed WRF. The clinical characteristics of the patients with and without WRF have been presented in Table 1. Accordingly, patients with WRF were older and presented

with more severe congestive symptoms. Atrial Fibrillation (AF) rhythm was also more frequently detected in these patients. Although the median (IQR) of serum Cr level on admission was within normal limits [1.2 (1 - 1.5)], about 19% of the study population's serum Cr levels were more than 1.5 mg/dL. WRF was also more frequently seen in these patients (28% versus 13%, $P = 0.006$). However, the results indicated no significant differences between the two groups with and without WRF in terms of blood pressure, heart rate, and LVEF on presentation. It should be noted that Cr levels returned to the baseline values in 21 patients (31.3%) who had developed WRF.

4.2. Predictors of WRF

The results of univariate analysis revealed older age, presence of AF rhythm, ascites, severe peripheral edema, high pro BNP level, and high serum Cr level on admission as the predictors of WRF in the setting of AHF. Then, binary multivariable logistic regression model was run to investigate the association between WRF and different predictors. The results demonstrated that serum Cr level on admission (baseline Cr level) and presence of ascites

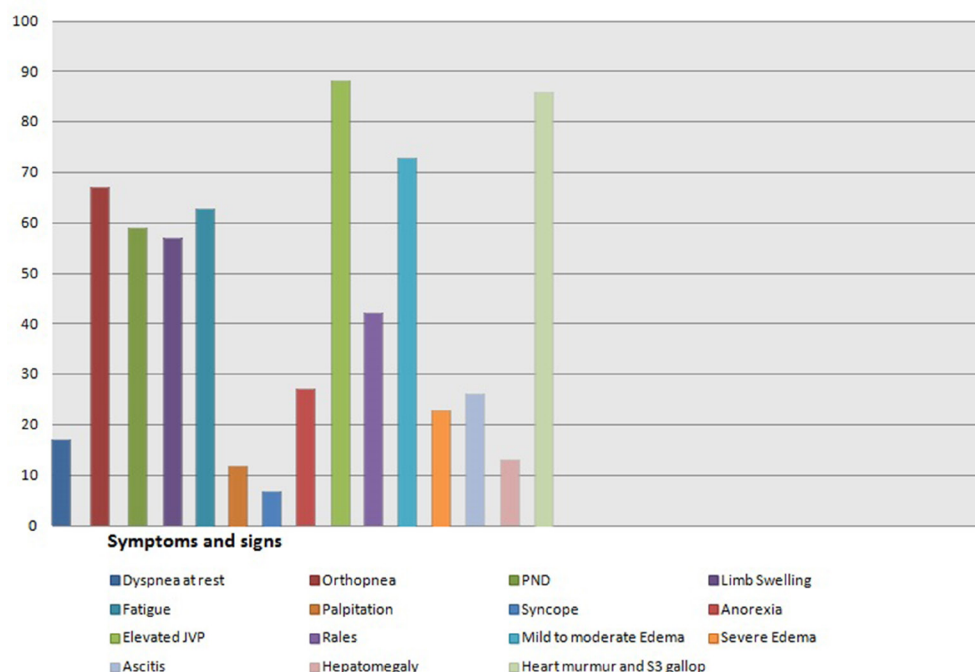


Figure 1. The Frequency of Symptoms and Signs in the Study Population (n = 230)

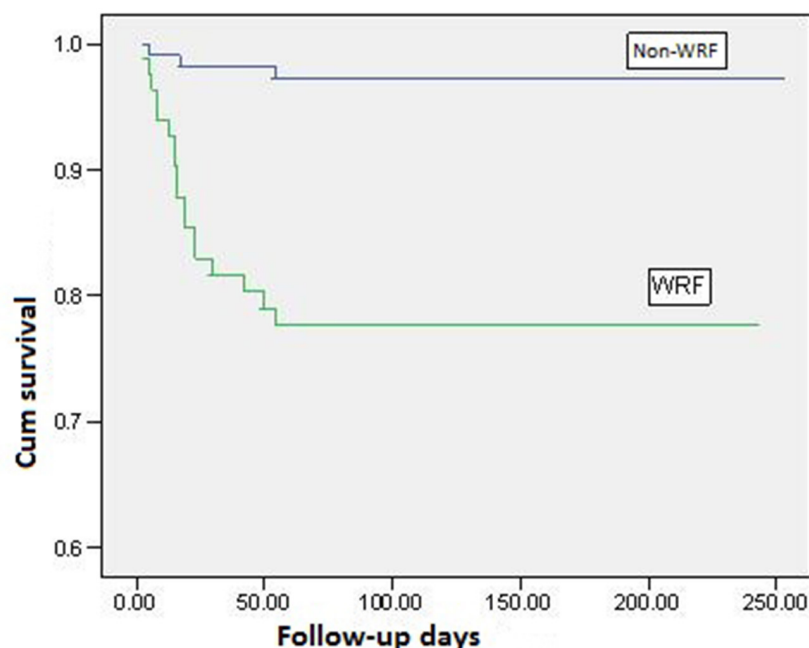


Figure 2. Kaplan-Meier Survival Analysis for Death during the Follow-up Period

were independent predictors of WRF in the patients with AHF. Indeed, baseline Cr level was a stronger predictor [$\beta = 0.7$, $P = 0.007$, OR (95% CI) = 1.94 (1.2 - 3.2) for baseline Cr level versus $\beta = 0.8$, $P = 0.03$, OR (95% CI) = 2.1 (1.05 - 4.4) for ascites].

4.3. Hospitalization Duration and Mortality

Based on Table 1, the length of hospital stay was significantly higher among the patients with WRF compared to the other patients (median of 14 days versus 8 days, $P < 0.001$). Additionally, in-hospital mortality rate and death within the 3-month follow-up was 23.9% and 19.4%, respectively in the patients with WRF, which were significantly higher in comparison to those without WRF ($P < 0.001$). Interestingly, mortality rate was significantly lower in the patients whose Cr levels had returned to baseline (23.8% versus 52.2%, $P = 0.03$).

The results of binary multivariable logistic regression analysis showed that WRF, presence of ascites, and lower SBP were independent predictors of in-hospital mortality (Table 3), with WRF being a stronger predictor.

The independent predictors of mortality 3 months after discharge have also been presented in Table 3. As the table depicts, presence of ascites, NYHA class on admission, and

baseline Cr > 1.5 mg/dL were the independent predictors of mortality due to AHF three months after discharge. Although in-hospital and post-discharge mortality were more prevalent in the patients with WRF, the two groups were not statistically different with respect to the re-hospitalization rate.

5. Discussion

The present study aimed to evaluate the prevalence and prognostic significance of WRF among hospitalized patients complicating acute systolic heart failure. The principal finding of the study was that during hospitalization, about 29% of the patients with AHF developed WRF (defined by increase in serum Cr > 0.3 mg/dL), which increased both length of hospital stay and mortality. Increase in serum Cr > 0.3 mg/dL from admission is the best gradation of renal deterioration, and this definition has also been utilized in prior studies (2, 3, 9, 10). However, some investigators have used a rise in serum Cr level above a threshold, a percentage of increase from baseline (e.g., 25% increase), or a combination of these two factors (4, 11) to define WRF. The previous studies showed the incidence of WRF in about one thirds of the admitted patients with AHF during hospitalization (2-4), which is similar to the current study.

Table 3. Independent Predictors of In-hospital Mortality and Mortality 3 Months after Discharge

Predictors of in-hospital mortality			
	Beta	P value	OR (95% CI)
WRF	1.7	0.001	5.6 (2 - 15)
Ascitis	1.2	0.01	3.3 (1.2 - 8.7)
SBP	0.03	0.03	0.9 (0.9 - 1)
Predictors of mortality 3 months after discharge			
NYHA class	1.5	0.001	0.2 (0.09 - 0.5)
Ascitis	0.7	0.04	0.5 (0.2 - 0.9)
Creatinine > 1.5 , mg/dL	1.7	< 0.001	0.19 (0.08 - 0.5)

Abbreviations: NYHA, New York heart association; SBP, systolic blood pressure; WRF, worsening renal function

Renal dysfunction is common in patients with heart failure. Indeed, occurrence of WRF during AHF therapy in the setting of persistent congestion has been associated with poor outcomes in a variety of observational studies (5, 9, 12-14). WRF is an important clinical phenomenon complicated by multiple pathophysiological mechanisms, which occurs either de novo or in the setting of a pre-existing chronic kidney disease among patients with AHF. However, in the setting of hospitalization for AHF, WRF is more important than baseline renal function for predicting adverse outcomes (15). In our study, WRF was more prevalent among 19% of the patients who had pre-existing chronic kidney disease at the time of admission. The precise pathophysiological mechanisms of WRF in patients with AHF are unclear. Acute cardiac and renal congestion, neurohormonal activation, dysregulation of immune cell and cytokine signaling, superimposed infection, anemia, failure of normal counter-regulatory systems, and activation of inflammatory cascades and oxidative stress accompanied with patients' characteristics and comorbid diseases, such as baseline renal dysfunction, diabetes mellitus, and hypertension, could lead to progressive and combined cardiac and renal dysfunction (16). Interestingly, some researchers believed that WRF was more likely a marker of greater heart failure severity than a mechanism contributing to its progression (14).

Up to now, multiple reports have focused on variables associated with WRF, including male gender, old age, history of pre-existing heart failure, pre-existing renal failure, diabetes, anemia, hypertension, larger drop in blood pressure, and high doses of diuretics (9, 14). Similarly, the current study findings revealed that older patients, those with higher levels of serum Cr on admission, and those who had more severe congestive symptoms were more prone to development of WRF in the setting of AHF. Additionally, presence of AF rhythm, ascites, severe peripheral edema, and high pro BNP levels were the predictors of WRF in the univariate analysis. Moreover, the results of binary multivariable logistic regression model showed that serum Cr level on admission and presence of ascites were the independent predictors of WRF. Yet, baseline serum Cr level was a stronger predictor among the patients with WRF. The previous studies also demonstrated that increase in intra-abdominal pressure in critically ill patients was associated with intra-abdominal organ dysfunction (17-19). Thus, ascites and visceral edema might cause elevated intra-abdominal pressure in patients with AHF and lead to WRF (20, 21). Mullens et al., too, disclosed that elevated intra-abdominal pressure was associated with WRF, which is in agreement with our findings. In the setting of intensive medical therapy for AHF, reduction in intra-abdominal pressure improved renal function in patients with baseline elevated intra-abdominal pressure. However, changes in intra-abdominal pressure or renal function were not correlated to changes in any hemodynamic variable (20).

The results of the present study indicated that presence of ascites in patients with AHF was associated with in-hospital and 3-month mortality. Elevated baseline serum Cr levels and occurrence of WRF in patients with AHF during hospitalization were associated with increase in the

length of hospital stay, in-hospital and long-term mortality, and re-hospitalization rates in the previous studies (4, 9, 10, 12, 22-24). Similar to the prior studies, our study results demonstrated that WRF during hospitalization was associated with increase in the length of hospital stay (14 days versus 8 days; $P < 0.001$), in-hospital mortality (16% versus 8%; $P < 0.001$), and mortality during the 3-month follow-up (13% versus 22%; $P < 0.001$). However, the results of binary multivariable logistic regression analysis indicated that WRF was only associated with in-hospital mortality. Interestingly, the patients whose Cr levels returned to baseline showed a lower mortality rate during the 3-month follow-up. This finding supports the PROTECT study results, in which Valente et al. (25) showed that WRF was not always associated with poor outcome, a pseudo-WRF was seen following adequate decongestion, and prognosis was favorable in patients who showed a good diuretic response and improvement in kidney function despite early rise in serum Cr level.

5.1. Study Limitations

One of the strengths of this study was the use of a dedicated software for data collection. Thus, all data were collected accurately with only a few missing data. However, like any observational study, unmeasured confounders might have existed. Another study limitation is related to the study population. This single-center study was conducted in a tertiary center and many of the patients had advanced heart failure. Hence, the results cannot be simply generalized to other centers. Thus, a multi-center study needs to be designed considering the experiences and results of this study for better evaluation of Iranian patients with AHF.

In conclusion, WRF was very common in the patients with AHF and was associated with higher in-hospital mortality and decrease in early survival after discharge. Generally, data obtained from registries in any country will be helpful for regional cardiologists to identify the limitations and deficiencies in management of patients with heart failure. Similarly, they can be quite useful for administrative programs in different aspects of treatment of heart failure patients in Iran.

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Authors' Contribution

Mohammad Hossein Soltani: Development of the idea for the research, data collection, review of the literature, and drafting the manuscript; Mohammad Javad Alemzadeh-Ansari: Review of the literature and drafting the manuscript; Sepideh Taghavi: Data collection; Behshid Ghadrdoost: Data collection and statistical analysis; Majid Maleki: Organizing and supervising the course of the project; Ahmad Amin: Data collection and interpretation of the results; Nasim Naderi: Development of the idea for the research, planning the methodology, organizing and

supervising the course of the project, and final edition of the manuscript

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