

## Clinical Study

# Worsening Renal Function in Patients Hospitalized with Acute Heart Failure: Risk Factors and Prognostic Significances

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**Objectives.** To determine the prevalence, the clinical predictors, and the prognostic significances of Worsening Renal Function (WRF) in hospitalized patients with Acute Heart Failure (AHF). **Methods.** 394 consecutively hospitalized patients with AHF were evaluated. WRF was defined as an increase in serum creatinine of  $\geq 0.3$  mg/dL from baseline to discharge. **Results.** Nearly 11% of patients developed WRF. The independent predictors of WRF analyzed with a multivariable logistic regression were history of chronic kidney disease ( $P = .047$ ), age  $>75$  years ( $P = .049$ ), and admission heart rates  $\geq 100$  bpm ( $P = .004$ ). Mortality or rehospitalization rates at 1 month, 6 months, and 1 year were not significantly different between patients with WRF and those without WRF. **Conclusion.** Different clinical predictors at hospital admission can be used to identify patients at increased risk for developing WRF. Patients with WRF compared with those without WRF experienced no significant differences in hospital length of stay, mortality, or rehospitalization rates.

## 1. Introduction

In the setting of heart failure, baseline renal insufficiency is a common and well-established independent marker of poor prognosis [1–6]. Worsening Renal Function (WRF) during the hospitalization for Acute Heart Failure (AHF) occurs frequently and may also have a prognostic significance. Indeed, several studies have reported that even small changes in renal function are associated with longer length of hospital stay, increased in-hospital costs, higher in-hospital mortality, higher mortality, and rehospitalization rates at short and long term [7–12]. However, not all the published information agree that WRF is associated with a worse clinical outcomes [13, 14]. Moreover, not all the studies have adopted the same definition of WRF [7, 8, 10, 11, 13–15] and in most of them only short-term followup (in-hospital complications and 6-months follow-up) was carried on [9–11]. Lastly, the major part of the results is derived from retrospective analyses, and in several studies a multivariate analysis was not performed to identify the independent prognostic value of WRF [7, 10, 11, 15]. Therefore, the role that WRF plays in general HF population is still to be better validated.

The goal of this study is to determine the prevalence, the clinical predictors, and the prognostic significance of WRF in a consecutive series of hospitalized patients for AHF.

## 2. Materials and Methods

**2.1. Study Population.** We enrolled patients consecutively admitted for AHF at our Institute from October 2002 to May 2008. Criteria for inclusion were exacerbation of previously documented Heart Failure (HF) or new onset of AHF using standard Framingham criteria [16]. The only criterion for exclusion was the presence of terminal noncardiac illness that could influence short-term prognosis.

**2.2. Study Protocol.** The study was approved by the local Ethics Committee, and all patients gave informed consent to participate.

All patients underwent a complete clinical and laboratory examination at the time of hospital admission and at hospital discharge. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) equation. This has been shown to be the best

method for the indirect assessment of renal function in HF population [17–19]. WRF was defined as an increase in serum creatinine of  $\geq 0.3$  mg/dL from baseline to discharge (WRF(CRE)). This value was chosen because it has previously been demonstrated to have the maximum sensitivity and specificity to predict the prognosis [11].

In order to verify the prognostic value of WRF, the hazard ratios for death and rehospitalization were also assessed for a decline in eGFR  $\geq 20\%$  from baseline to discharge (WRF(GFR)) [20].

Followup was performed by clinical visits and/or telephone calls at 1 month, 6 months, and 1 year. The main endpoints were hospital length of stay, death, and rehospitalization risks.

**2.3. Statistical Analysis.** Continuous variables were expressed as the arithmetic mean and the standard deviation (SD). Discrete variables were presented as a percentage. Associations between WRF and continuous variables were analyzed using Student's *t*-test for normal data and Wilcoxon test for not normally distributed variables. Discrete Variables were compared with the use of Chi-square analysis. A forward stepwise multivariable logistic regression analysis was performed to identify the independent variables predictive of WRF. All the variables which were significantly different ( $P < .1$ ) between patients with and without WRF at univariable analysis were taken into multivariable analysis, but only retained at an exit significance value of  $P < .05$ . Associations of the development of WRF with the prognostic outcomes (hospital length of stay, hospitalization, and mortality risks) were assessed with a Cox proportional hazards analysis. Survival probability curves were constructed according to the Kaplan-Meier method.

### 3. Results

**3.1. Baseline Characteristics and Prevalence of WRF.** Patients' characteristics are presented in Table 1. We initially enrolled in the study 402 consecutive patients. Eight of them were lost to follow-up and were excluded from the analysis. No one of the lost to follow-up patients had developed the WRF during the index hospitalization. Therefore, the study population consists of 394 consecutive patients. The mean age of the cohort was 77.9 (SD 10.1) years, with nearly 70% of the patients over 75 years. The majority of the patients were male (67.5%). Almost 60% of the total population had a history of prior hypertension (58.4%), heart failure (61.7%), and acute coronary syndrome (57.4%). Relatively high percentages of diabetes (33%) and anemia (42.4%) were present in the population. The mean ejection fraction was 39.6% (SD 12.2) with 241 patients (61.2%) having EF  $< 45\%$ . On admission, 159 (40.3%) patients were in NYHA class IV, 194 (49.2%) patients were in NYHA class III, and only 41 (10.4%) patients were in NYHA class II. At time of the admission, more than half of the patients were on diuretics (72.3%) and on ACE inhibitors (54.7%) treatments; 109 (27.7%) patients were receiving beta-blockers. The mean serum creatinine was 1.5 (SD 0.8) mg/dL with 111 (28.2%)

of the patients having values  $> 1.5$  mg/dL. WRF(CRE) and WRF(GFR) occurred, respectively, in 10.9% and in 11.6% of the population.

**3.2. Predictors of WRF.** In the univariable analysis, patients who experienced WRF(CRE) compared with those without WRF(CRE) were more likely to be older than 75 years, to have a history of preexisting Chronic Renal Failure (CRF), and to have higher heart rate (atrial or sinus arrhythmia with a heart rate  $> 100$  bpm). Higher serum creatinine (Scr) level and lower eGFR value at admission were also found to be significantly associated with the development of WRF. Moreover, patients with WRF(CRE) were more likely to be on calcium channel blockers and less likely to be on digoxin treatment. There were no significant differences in the other considered variables.

When a multivariable analysis was conducted (results listed in Table 2), preexisting CRF, admission heart rate ( $\geq 100$  bpm), and age ( $> 75$  years) remained independent risk factors for the development of WRF(CRE) (resp.,  $P = .047$ ;  $.004$ ;  $.049$ ). Conversely, digoxin treatment resulted to have a protective effect against WRF(CRE) ( $P = .024$ ).

**3.3. WRF and Prognosis.** The mean hospital length of stay during the index hospitalization was  $8.8 \pm 4.8$  days [median: 7 days; interquartile range(iqr): 6–10] for the whole group. Patients who develop WRF(CRE) and patients without WRF(CRE) were similar in mean and median hospital length of stay (resp., mean:  $8.5 \pm 4.3$  days; median: 7 days; iqr: 6–10; Versus mean:  $8.9 \pm 4.9$  days; median: 7 days; iqr: 6–10;  $P = .64$ ). Patients with and patients without WRF(GFR) experienced no significant differences in hospital length of stay (resp., mean:  $8.0 \pm 3.6$  days; median: 7 days; iqr: 5–10; Versus mean:  $8.9 \pm 5$  days; median: 7 days; iqr: 6–10;  $P = .29$ ).

There were no statistically significant differences in rehospitalization risk between patients with WRF(CRE) and patients without WRF(CRE) at either 1 month, 6 months, or 12 months (results shown in Table 3). Patients with WRF(CRE) experienced no significantly higher risk of death at 1-, 6-, and 12-month followup (Table 3).

Similar results were observed when the WRF(GFR) definition was adopted (results shown in Table 4).

The combined endpoint death/rehospitalization was considered for the construction of Kaplan-Meier survival-free curves of patients with and without WRF(CRE). As it is possible to observe in Figure 1, the two curves were almost similar (log-rank test:  $P = .947$ ).

### 4. Discussion

Several previous studies have reported a relatively high prevalence of WRF (around 25%) among patients hospitalized with acute heart failure [10, 12, 14, 21]. In our study, the prevalence of WRF is lower (11%). This is probably due to the fact that in our study patients with a transitory increase in Scr or decrease in eGFR, which did not persist at the moment of discharge, were not considered as WRF-patients.

TABLE 1: Characteristics at admission of the whole population and of patients with and without WRF (CRE).

	Total (n = 394)	WRF absent (n = 351)	WRF present (n = 43)	P-value
<b>Demographics</b>				
Age (mean, SD)	77.9 (10.1)	77.8 (10.3)	79.2 (8.4)	.380
Age > 75 years	274 (69.5)	239 (68.1)	35 (81.4)	.074
Males	266 (67.5)	236 (67.2)	30 (69.8)	.738
<b>Medical history</b>				
Prior heart failure	243 (61.7)	218 (62.1)	25 (58.1)	.613
Diabetes	130 (33.0)	108 (30.8)	12 (27.9)	.700
Valvular disease	108 (27.4)	99 (28.2)	9 (20.9)	.313
COPD	122 (30.9)	111 (31.6)	11 (25.6)	.418
Hypertension	230 (58.4)	201 (57.3)	29 (67.4)	.201
Peripheral vascular disease (PVD)	74 (18.8)	67 (19.1)	7 (16.3)	.656
Previous acute coronary syndrome	226 (57.4)	204 (58.1)	22 (51.2)	.384
Prior renal failure	95 (24.1)	76 (21.6)	19 (44.2)	.001
<b>Clinical and laboratory parameters</b>				
Systolic blood pressure, mm Hg (mean, SD)	132 (25.5)	131 (25.1)	137 (29.1)	.138
Systolic blood pressure >160 mm Hg	43 (10.9)	36 (10.3)	7 (16.3)	.230
Serum creatinine, mg/dL (mean, SD)	1.5 (0.8)	1.47 (0.8)	1.71 (0.9)	.066
Creatinine > 1,5 mg/dL	111 (28.2)	92 (26.2)	19 (44.2)	.013
GFR, mL/min (mean, SD)	54 (23.5)	55 (22.8)	51 (28.4)	.070
GFR < 60 mL/min	239 (60.7)	207 (59.0)	32 (74.4)	.055
Sodium, mEq/L (mean, SD)	140 (4.4)	140 (4.5)	140 (3.5)	.854
Potassium, mEq/L (mean, SD)	4.0 (0.6)	4.0 (0.6)	3.9 (0.6)	.219
Glycemia, mg/dL (mean, SD)	76 (73.0)	78 (74.6)	58 (56.6)	.114
Haemoglobin, gr/dL (mean, SD)	12.6 (6.5)	12.7 (1.8)	12.1 (6.9)	.387
Anaemia (hemoglobin <12 gr/dL)	167 (42.4)	147 (41.9)	20 (46.5)	.562
Haematocrit (mean, SD)	38 (6.1)	39 (6.2)	38 (5.2)	.502
Azotemia, mg/dL (mean, SD)	46 (50.0)	45.5 (49.1)	50.2 (60.5)	.561
NYHA class (mean, SD)	3.3 (0.7)	3.3 (0.6)	3.3 (0.7)	.778
NYHA class III-IV	353 (89.6)	316 (90.0)	37 (86.0)	.420
KILLIP (mean, SD)	2.4 (0.6)	2.3 (0.6)	2.4 (0.6)	.363
<b>Doppler echocardiography</b>				
Ejection fraction (mean, SD)	39.6 (12.2)	39.5 (12.2)	39.7 (12.4)	.942
Ejection fraction <45%	241 (61.2)	215 (61.3)	26 (60.5)	.869
Left atrial size, mm (mean, SD)	46.3 (7.3)	46.4 (7.5)	45.2 (6.0)	.343
Left ventricular size, mm (mean, SD)	58.5 (9.5)	58.4 (10.0)	58.1 (6.7)	.982
Left atrial dilatation	232 (58.9)	211 (60.1)	21 (48.8)	.279
Left ventricular dilatation	265 (67.3)	237 (67.5)	28 (65.1)	.880
<b>Elettrocardiogram</b>				
LBBB	45 (11.4)	40 (11.4)	5 (11.6)	.960
Heart rate, bpm (mean, SD)	85.3 (17.0)	85 (17.0)	88 (16.3)	.276
Heart rate ≥ 100 bpm	80 (20.3)	64 (18.2)	16 (37.2)	.003
Atrial fibrillation	164 (41.6)	149 (42.4)	15 (34.9)	.342
<b>Medical treatments</b>				
Aldosterone antagonists	88 (22.3)	76 (21.6)	12 (27.9)	.352
Diuretics	285 (72.3)	255 (72.5)	30 (69.8)	.690
Beta-blockers	109 (27.7)	98 (27.9)	11 (25.6)	.746
Calcium channel blockers	60 (15.3)	49 (14.0)	11 (25.6)	.045
ACE inhibitors	215 (54.7)	190 (54.1)	25 (58.1)	.618
ARBs	37 (9.4)	30 (8.5)	7 (16.3)	.101
Statins	46 (11.7)	40 (11.4)	6 (14.0)	.865
ASA	163 (41.4)	143 (40.7)	20 (46.5)	.468
Warfarin	101 (25.6)	91 (25.9)	10 (23.3)	.705
Nitrates	144 (36.5)	133 (37.9)	11 (25.6)	.114
Digoxin	99 (25.1)	95 (27.1)	4 (9.3)	.006

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; ASA: acetylsalicylic acid; LBBB: left bundle branch block; COPD: chronic obstructive pulmonary disease; NYHA: New York Health Association.

TABLE 2: Predictors of WRF (CRE): multivariable analysis.

Predictors	Odds ratio	95% CI	P-value
Age > 75 years	2.34	1.00–5.46	.049
Calcium channel blockers	1.53	0.68–3.44	.300
Creatinine > 1,5 mg/dL	0.90	0.33–2.50	.840
Digoxin	0.29	0.10–0.85	.024
Prior renal failure	2.80	1.01–7.79	.047
Heart rate $\geq$ 100 bpm	2.89	1.40–5.94	.004

CI: Confidence Interval.

TABLE 3: Association of WRF (CRE) with mortality and rehospitalizations risks.

	HR	95% CI	P-value
<b>Mortality</b>			
1 month	1.01	0.13–8.07	.99
6 months	0.80	0.32–1.99	.63
12 months	1.03	0.49–2.15	.94
<b>Rehospitalization</b>			
1 month	1.32	0.51–3.38	.56
6 months	1.00	0.59–1.70	.99
12 months	1.02	0.63–1.63	.95

CI: Confidence Interval.

TABLE 4: Association of WRF (GFR) with mortality and rehospitalizations risks.

	HR	95%	P-value
<b>Mortality</b>			
1 month	0.93	0.12–7.43	.94
6 months	0.89	0.38–2.08	.79
12 months	1.09	0.54–2.12	.81
<b>Rehospitalization</b>			
1 month	1.21	0.47–3.01	.69
6 months	0.82	0.47–1.43	.48
12 months	0.89	0.55–1.43	.63

CI: Confidence Interval.

The mechanisms which may cause WRF in patients with HF are multiple and are not completely understood [22]. Several predictors of WRF have been reported in the literature. One of the most acknowledged predictors is renal dysfunction either as a preexisting renal disease or as admission renal failure [8, 9, 13]. In a retrospective study carried on by Forman et al [10] on more 1000 patients, history of prior chronic heart failure, diabetes, systolic blood pressure >160 mmHg, and serum creatinine >1.5 mg/dL were identified as the most important predictors of WRF and used to elaborate a score to stratify the risk of developing WRF. Other reported important risk factors of WRF were: advanced age [7, 21], high systolic blood pressure [10, 14], diabetes [8, 10, 14], pulmonary edema [13], NYHA class [8], ejection fraction [8], use of high doses of furosemide [8, 9], and use of calcium channel blockers [9].

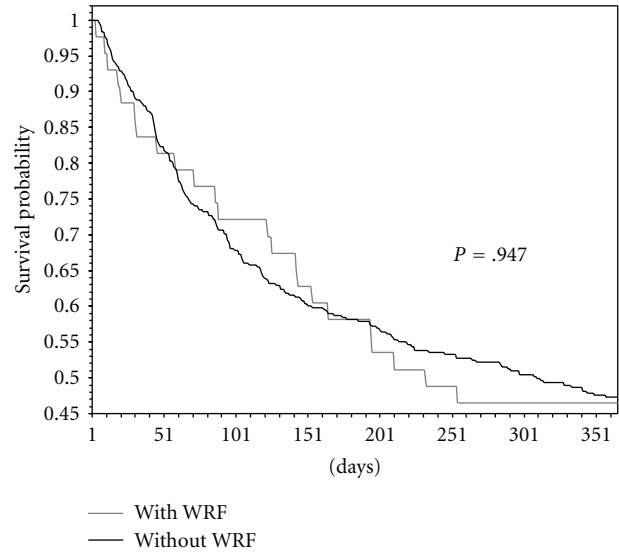


FIGURE 1: Kaplan-Meier hospitalization and mortality free survival curves for patients with and without WRF.

In our study, we report that the history of preexisting renal failure is one of the strongest independent predictors of WRF. The age was found to be another independent predictor of WRF. Patients who are >75 years old were more likely to develop WRF.

In the univariable analysis, baseline serum creatinine and baseline eGFR were associated with WRF; however these links disappeared when the multivariable analysis were conducted. Although the results of some studies [10, 13] are not consistent with these findings, in the ESCAPE study baseline renal insufficiency was not predictive of WRF even in the univariable analysis [14], and similar results were observed in the prospective study of Metra et al. [8].

In our investigation, digoxin use was shown to have a protective effect against WRF. This result has not been reported previously. The effect does not disappear on multivariable analysis. Since the small number of patients on digoxin use, this observation is likely to be due only to chance.

Heart rate >100 bpm was another independent risk factor of WRF that was not previously reported. This finding may be due to an underlying more severe cardiac disease or to an underuse of medications in these patients.

Worsening renal function during the hospitalization for acute heart failure has been shown to be associated with lengthier hospitalization. However, in our study, the patients with WRF had almost equal mean hospital length of stay to those who did not develop WRF.

Similar short- and long-term rehospitalization and mortality rates were found in patients with and without WRF. Similar findings were observed adopting both definitions of WRF (WRF(CRE) and WRF(GFR)) to assess the prognostic significance of WRF. These data are in agreement with the results reported in a European multicenter prospective study (POSH study) [13] and in the ESCAPE study [14]. On the other hand, several studies have reported that even



small changes in serum creatinine during the hospitalization for acute heart failure are associated with higher rehospitalization risk and mortality rate. These conflicting results highlight the need of a better comprehension of the prognostic significances of WRF in patients with AHF. The fear of WRF may have important clinical consequences, since the physicians could tend to reduce diuretics dosages and to underuse important life-prolonging drugs such as aldosterone antagonists and ACE inhibitors.

Further prospective studies are needed to elucidate whether WRF, in the setting of AHF, is a justified fear or just a marker of intrinsic renal disease that is inevitable in patients with several risk factors.

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