Original Article

Prognostic Value of Worsening Renal Function in Patients with Acute Decompensated Heart Failure with Preserved Ejection Fraction and its Association with Increased Inflammatory State

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Abstract

Objective: The prognostic impact of worsening renal function (WRF) in patients with acute decompensated heart failure (ADHF) with preserved ejection fraction is controversial, and the pathophysiological mechanisms of WRF are not clearly understood. **Methods:** Fifty-three patients with ADHF with preserved ejection fraction were analyzed. WRF was defined as an increase of ≥ 0.3 mg/dL in the serum creatinine level during the first 5 days of the hospitalization and occurred in 37.7% of the study population. **Results:** Although baseline C-reactive protein (CRP) levels on admission was similar between patients with and without WRF, patients with WRF had higher 48-h CRP and delta CRP (Δ−CRP = 48-h CRP value − baseline CRP value) levels than those of patients without WRF. Multivariable analysis revealed that the baseline creatinine level and Δ−CRP were the independent risk factors for the development of WRF. The length of hospital stay (LOS) was significantly longer in the WRF group (9.9 ± 10.2 vs. 5.4 ± 2.8 days; $P = 0.020$). The median follow-up of the study population was 683 days, and the all-cause mortality rate was higher in patients with WRF than those without WRF (40% vs. 9.1%, $P = 0.007$, respectively). **Conclusion:** Baseline creatinine levels and Δ−CRP were the independent predictors of WRF. Increased inflammatory status expressed by Δ−CRP is found to be a novel finding for predicting the development of WRF in patients with ADHF with preserved ejection fraction. The presence of WRF was found to be associated with a poorer prognosis, including longer LOS, higher all-cause in-hospital, and all-cause postdischarge mortality.

Keywords: Acute decompensated heart failure, C-reactive protein, heart failure with preserved ejection fraction, kidney, worsening renal function

Introduction

Renal dysfunction is a frequent and important problem in patients with congestive heart failure (HF). The presence of renal dysfunction is associated with adverse outcomes, and renal dysfunction is an independent predictor of mortality in patients with HF.[1,2] Worsening renal function (WRF) is defined as an increase of ≥ 0.3 mg/dL in serum creatinine level compared with the value on admission.[3,4] The registry data reveals that more than half of patients with HF with preserved ejection fraction (HFpEF) have WRF during the hospitalization period.[5] In the setting of acute decompensated HF (ADHF),

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WRF is associated with a prolonged length of intensive care unit and/or hospital stay (LOS), increased hospital mortality and morbidity, and higher rates of rehospitalization and death after discharge from the hospital.[5-12] However, some clinical studies do not confirm these results.[13,14] Therefore, the prognostic impact of WRF in patients with ADHF is still controversial. On the other hand, several mechanisms are proposed regarding WRF in patients with HF; however, the pathophysiological mechanisms of WRF in patients with HF, especially HFpEF, are not clearly understood.[15]

The aim of the present study is to determine the frequency, predictors, and prognostic significance of WRF in hospitalized patients with HFpEF. In addition, we investigated the association between WRF and increased inflammatory status expressed by C-reactive protein (CRP) in these patients.

Methods

Study population

We analyzed 190 patients with ADHF who were admitted to the intensive cardiac care unit (ICCU) of Başkent University İstanbul Hospital between January 2016 and April 2018. ADHF was diagnosed based on the presence of typical symptoms (dyspnea, orthopnea, and/or paroxysmal nocturnal dyspnea) and signs (pulmonary and/or peripheral congestion) with the need for intravenous furosemide administration. HFpEF was diagnosed based on the recommendations of current HF guidelines as follows: (i) Left ventricular ejection fraction (LVEF) ≥50%, (ii) elevated levels of natriuretic peptides, (iii) diastolic dysfunction, left ventricular hypertrophy, and/or left atrial enlargement.[16,17] Patients' medical data were retrospectively retrieved from the electronically stored medical information records of our hospital.

Patients with HF with reduced ejection fraction (HFrEF) or HF with mid-range ejection fraction (HFmrEF) (n = 71 patients); patients with acute coronary syndrome or ventricular arrhythmias (n = 30 patients); patients with sepsis and/or systemic infection with the need for intravenous antibiotic therapy, positive blood, urine culture test, and/or fever ≥ 38°C (n = 24 patients); and patients without adequate CRP data (n = 12 patients) were excluded from the study. As a result, the study population consisted of 53 patients with HFpEF who were hospitalized for ADHF [Figure 1].

Investigations

All study populations underwent a clinical and laboratory examination at the time of hospital admission. Patients' clinical data, including demographic features, comorbidities, cardiovascular risk factors, and HF medications, were recorded on electronic case report forms. Blood urea nitrogen and creatinine levels were assessed at the time of hospital admission, and on the 2nd, 3rd, and 5th day of hospitalization. In addition, CRP levels were assessed at the time of hospital admission and 48 h later, according to our standard "ICCU – Patient Monitoring Protocol." A trans-thoracic echocardiographic examination was performed in all patients within 48 h of admission. All patients

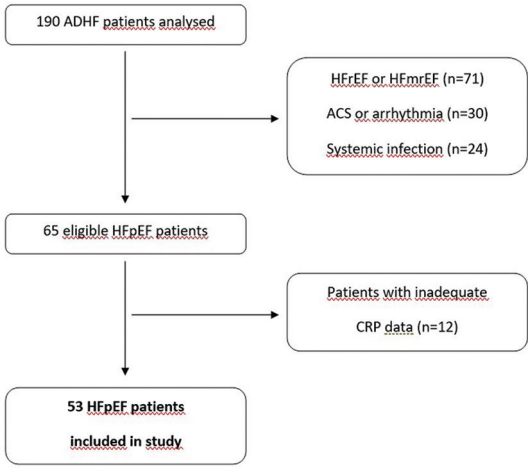

Figure 1: Flow chart of the study (ADHR: Acute decompensated heart failure, HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, ACS: Acute coronary syndrome, HFpEF: Heart failure with preserved ejection fraction, CRP: C-reactive protein)

received prespecified, standardized decongestive HF therapy as a part of "ICCU– Acute HF Treatment Protocol."

Definitions

WRF was defined as an increase of ≥ 0.3 mg/dL in serum creatinine level during the first 5 days of the hospitalization period compared with the value on hospital admission.[3,4] The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation.[18] Chronic kidney disease (CKD) was defined based on a ≥ 3-month history of an eGFR < 60 mL/min/1.73 m^2.[19]

Follow-Up

The first hospital admission was considered the index hospitalization for patients who were rehospitalized during the follow-up period after their discharge. All study patients were followed with outpatient clinical visits. The frequency of follow-up outpatient visits was determined by the patient's physician. The short-term outcomes were defined as the length of ICCU stay and in-hospital all-cause death. The long-term prognosis was defined as all-cause death during the follow-up period after hospital discharge. The median follow-up of the whole study population was 683 days.

Statistical analyses

A statistical analysis was performed using the Statistical Package for the Social Sciences software (version 17.0, SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were described as the mean ± standard deviation (P > 0.05 in Kolmogorov–Smirnov test or Shapira-Wilk test [n < 30]). Nonnormally distributed continuous variables were described as the median and range. Comparisons between groups were applied using the Student t-test (group: patient and control) or one-way analysis of variance (group: Patient and other and control) for normally distributed data. Mann–Whitney U-test or Kruskal-Wallis test was used for the nonnormally

distributed data. The categorical variables between the groups were analyzed by using the Chi-square test or Fisher's exact test. A multiple logistic regression analysis-stepwise method was used to know the associations between measurements with group as dependent variable. Values of $P < 0.05$ were considered statistically significant.

Results

Patients' baseline characteristics

The study included 53 hospitalized patients with HFpEF. The baseline characteristics of the study population are presented in Table 1. The mean age of patients was 79 ± 10 years, and 54.7% of patients were males. The etiology of HF was ischemic in 43.4% of patients, and 30.2% of the cases had a history of acute myocardial infarction. All the study population patients were in the New York Heart Association (NYHA) Class III or IV (73.5% and 26.5%, respectively), and their mean LVEF on echocardiographic examination was 55% ± 4%. The mean duration of HF was 7.1 ± 5.6 years before the study, and 69.8% of patients had a history of hospitalization because of ADHF.

The most frequent comorbidities were hypertension (86.8%), atrial fibrillation (62.3%), CKD (58.5%), anemia (58.5%), coronary artery disease (49.1%), chronic lung disease (37.7%), and diabetes mellitus (26.4%). At the time of hospital admission, more than two-thirds of patients were being treated with diuretics (73.6%) and beta-blockers (69.8%) treatments, 26 (49.1%) patients were receiving renin-angiotensin system inhibitors, and 12 (22.6%) patients were receiving mineralocorticoid receptor antagonists. On admission, the mean serum creatinine level was 1.87 ± 1.2 mg/dL, and mean eGFR was 45 ± 26 mL/min/1.73 m^2 [Table 1].

Frequency and predictors of worsening renal function

During the first 5 days of the hospitalization period, WRF occurred in 37.7% of the study population. Demographic features, comorbidities, cardiovascular risk factors, the usage rate of HF medications, and laboratory analyses at the time of hospital admission, including blood urea nitrogen and eGFR were similar between patients with and without WRF [Table 1]. Patients with WRF had higher baseline creatinine (2.24 ± 1.6 mg/dL vs. 1.64 ± 0.9 mg/dL; $P = 0.046$) and higher N-terminal pro-B-type natriuretic

Table 1: Patients' baseline characteristics according to the presence of worsening renal function

Variables	Total (n=53)	No WRF (n=33, 62.3%)	WRF (n=20, 37.7%)	P
Age (years)	79.9±10.8	80.5±8.8	78.9±13.6	0.605
Males (%)	54.7	48.5	65	0.242
Ejection fraction (%)	55.3±4.2	55±3.7	55.8±5	0.508
Coronary artery disease (%)	49.1	39.4	65	0.071
Hypertension (%)	86.8	87.9	85	0.764
Diabetes mellitus (%)	26.4	27.3	25	0.856
Atrial fibrillation (%)	62.3	69.7	50	0.152
Chronic kidney disease (%)	58.5	51.5	70	0.186
Chronic respiratory disease (%)	37.7	45.5	25	0.136
Anemia (%)	58.5	51.5	70	0.186
Cerebrovascular disease (%)	9.4	12.1	5	0.390
Peripheral artery disease (%)	17	18.2	15	0.765
RAS – inhibitors (%)	49.1	42.4	60	0.215
Beta-blockers (%)	69.8	66.7	75	0.522
MRAs (%)	22.6	24.2	20	0.721
Diuretics (%)	73.6	72.7	75	0.856
Statins (%)	22.6	18.2	30	0.319
BUN (mg/dL) (on admission)	47.8±21.6	39.5±20.4	48.2±22.9	0.157
BUN (mg/dL) (peak)	54.2±28.3	42.8±24.4	72.6±24.8	<0.001
Creatinine (mg/dL) (on admission)	1.87±1.2	1.64±0.9	2.24±1.6	0.046
Creatinine (mg/dL) (peak)	2.29±1.5	1.66±0.9	3.32±1.9	<0.001
Δ – Creatinine (mg/dL)	0.45±0.7	0.07±0.1	1.08±1	<0.001
GFR (mL/min) (on admission)	45.3±26.2	48.9±27.3	40±24	0.235
GFR (mL/min) (nadir)	39.2±24.8	48.4±25.1	23±13.7	<0.001
Δ –GFR (%)	21.3±24.6	10.7±22.1	38.8±17.8	<0.001
Hemoglobin (mg/dL)	11.2±2	11.4±2	10.9±1.9	0.373
NT-proBNP (on admission) (pg/mL)	9905±10816	7422±8924	13879±12534	0.033
CRP (mg/dL) (on admission)	39.3±40.9	36.5±41.1	43.7±41.2	0.540
CRP (mg/dL) (peak)	67±66.8	48.2±49.8	96.1±79.7	0.009
Δ – CRP (mg/dL)	27±55.6	10.6±17	52.4±81.1	0.006

WRF: Worsening renal function, RAS: Renin–angiotensin system, MRAs: Mineralocorticoid receptor antagonists, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, NT-proBNP: N-terminal pro–B-type natriuretic peptide, CRP: C-reactive protein

peptide (NT-proBNP) (13879 ± 12534 pg/mL vs. 7422 ± 8924 pg/mL; P = 0.033) levels than those patients without WRF at the time of hospital admission. Although baseline CRP levels on admission were similar between patients with and without WRF, patients with WRF had higher 48-h CRP and delta CRP (Δ−CRP = 48-h CRP value − baseline CRP value) levels than those of patients without WRF [Table 1 and Figure 2]. Multivariable analysis revealed that the baseline creatinine level (odds ratio [OR]: 1.79; 95% confidence interval [CI]: 1.01–3.22; P = 0.04) and Δ−CRP (OR: 1.03; 95% CI: 1.01–1.06; P = 0.03) were the independent risk factors for the development of WRF [Table 2].

Prognostic impact of worsening renal function

The average LOS during index hospitalization was 7.1 ± 6.9 days for the study population. The LOS was significantly longer in patients with WRF than those without WRF (9.9 ± 10.2 days vs. 5.4 ± 2.8 days; P = 0.020, respectively). The all-cause in-hospital mortality rate was 7.5% for the whole population, and the all-cause in-hospital mortality rate was higher in the WRF group (0% vs. 20%; P = 0.008) [Table 3]. After hospital discharge, the 1-year survival rate was 96.9% for patients without WRF and 71.4% for patients with WRF (P = 0.01). The median follow-up of the study population was 683 days, and during the follow-up period, 11 patients died (20.8%), including three of the 33 (9.1%) patients without WRF, and eight of the 20 (40%) patients with WRF (P = 0.007) [Table 3 and Figure 3].

Table 2: Logistic regression analysis for the predictors of worsening renal function

Variables	OR	95% CI	*P*
Age	1.01	0.94–1.09	0.687
Creatinine (on admission)	1.79	1.01–3.22	0.049
GFR (on admission)	1.01	0.97–1.05	0.556
Δ – CRP (mg/dL)	1.03	1.01–1.06	0.036
NT-proBNP (on admission)	1.00	1.00–1.00	0.086

GFR: Glomerular filtration rate, CRP: C-reactive protein, NT-proBNP: N-terminal pro–B-type natriuretic peptide, CI: Confidence interval, OR: Odds ratio

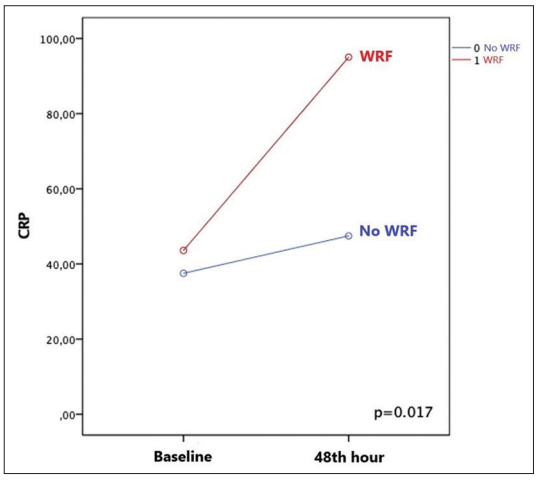

Figure 2: Time-dependent C-reactive protein change in worsening renal function and No worsening renal function groups (WRF: Worsening renal function, CRP: C-reactive protein)

Discussion

In the present study, we determined the frequency and predictors of WRF during the hospitalization period. In addition, we investigated the association between WRF and increased inflammatory status, as expressed by the Δ−CRP. We determined the prognostic value of WRF for short-and long-term outcomes, including LOS, all-cause in-hospital mortality, and all-cause postdischarge mortality.

The frequency of WRF varies on a large scale depending on the study population characteristics and the definition of WRF. WRF has been reported between 11% and 68% among hospitalized patients with ADHF.[6-9,20] In the present study, the frequency of WRF was 37.7%, which was similar to clinical studies that reported a high frequency of WRF in patients with ADHF, but higher than others that reported the frequency of WRF as 11%–16%.[4-7,12,21-24] The reasons for the high frequency of WRF in our study might be that the patient population was older, the proportion of patients with CKD was higher, and the baseline GFR values at the time of admission were lower compared with some of these studies.[6,12,24]

Complex and multifactorial pathophysiologic mechanisms play essential roles in the the development of WRF in patients with ADHF. The possible mechanisms that were proposed regarding the WRF in patients with ADHF include hypoperfusion of the kidney, central venous pressure elevation, activations of the renin-angiotensin system, sympathetic overactivity, endothelial dysfunction due to oxidative injury, and an inflammatory process.[25,26] Previously, the leading cause of WRF development in the course of HF was thought to be hypoperfusion of the kidney due to a decrease in cardiac output.[27] However, the opinion on this issue has shifted from this phenomenon to

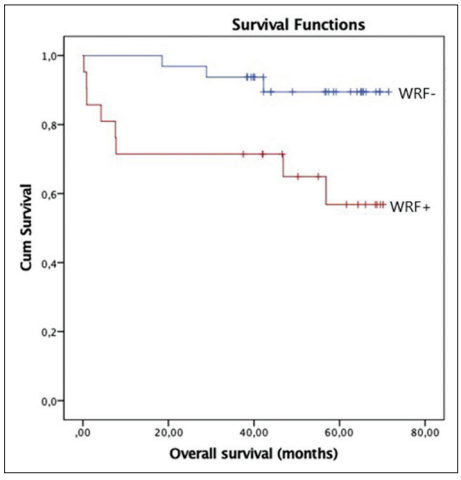

Figure 3: Kaplan–Meier survival curve for overall survival in heart failure with preserved ejection fraction patients with and without worsening renal function (HFpEF: Heart failure with preserved ejection fraction, WRF: Worsening renal function)

Table 3: Outcomes of patients with and without worsening renal function

	Total (n=53)	No WRF (n=33, 62.3%)	WRF (n=20, 37.7%)	P
Length of in-hospital stay (days)	7.1±6.9	5.4±2.8	9.9±10.2	0.020
All-cause in-hospital mortality (%)	7.5	0	20	0.008
All-cause postdischarge mortality (%)	20.8	9.1	40	0.007

WRF: Worsening renal function

other mechanisms, such as venous congestion, neurohumoral activation, and activation of an inflammatory condition.[3,9,28,29] Several clinical risk factors and predictors have been identified for the development of WRF in patients with ADHF. Age, NYHA class, diabetes, anemia, LVEF, the presence of renal dysfunction on admission, and baseline creatinine level were reported as the independent predictors of WRF.[4,7,13,14,30] In a retrospective, single-center study conducted in 1083 patients with ADHF, WRF was associated with high CRP and BNP levels on admission.[9] The Korean Acute HF registry was a prospective, multicenter center study conducted in 1295 patients with HFpEF. This study revealed that a history of CKD, anemia, hyponatremia, high NT-proBNP, and CRP > 0.5 mg/dL levels on admission were the independent predictors of WRF.[5] In accordance with previous studies, univariate analysis of our study demonstrated that high baseline serum creatinine, high Δ−CRP levels, and high baseline NT-proBNP were associated with WRF. In the multivariable analysis, baseline serum creatinine, and high Δ−CRP levels were the independent predictors of WRF. These results suggest that preexisting renal dysfunction and high serum creatinine levels on hospital admission are the important risk factors for the development of WRF in the setting of ADHF. On the other hand, the inflammatory process and its components are the important risk factors for the development of WRF in cardiovascular diseases, particularly after acute coronary syndromes and non-ST-segment elevation myocardial infarction.[31,32] An increased inflammatory state may also play a role in the worsening of HF by aggravating volume overload, thus leading to an elevation in venous pressure, acute kidney injury, and the reduction of glomerular filtration capacity.[26,33] In our study, as a novel finding, although baseline CRP levels were similar between patients with and without WRF, the significant increase in 48-h CRP levels in patients with WRF revealed that the inflammatory process had a significant role in the pathophysiological mechanisms of WRF in patients with ADHF.

Previous studies demonstrated that WRF during the hospitalization period for ADHF is associated with a longer LOS and in-hospital adverse outcomes, and WRF is an independent predictor of poor long-term prognosis for patients with ADHF.[5,7,8,10,20,34-37] For example, Metra *et al*.[7] found that patients with ADHF who developed WRF had a longer duration LOS (15 days vs. 8 days), and this result was confirmed by other clinical studies that included ADHF patients.[10,34] Cowie *et al*.[13] showed that the all-cause in-hospital mortality rate was higher in patients with WRF than in patients without WRF (12% vs. 2%, respectively). In a study of 200,063 hospitalized patients with ADHF, Kociol *et al*.[20] reported that the all-cause 1-year mortality rate was 35.4% in patients with WRF. Although the association between HF and WRF is important for both HF patients with HFrEF and HFpEF, this association has been suggested to be more critical in patients with HFpEF.[38,39] The KorAHF registry data revealed that WRF is an independent predictor of adverse outcomes in patients with HFpEF. According to the KorAHF registry, the development of WRF during the hospitalization period is associated with longer LOS and higher in-hospital and 1-year mortality rates. In addition, investigators highlighted that WRF is a prognostic factor for adverse in-hospital and long-term outcomes, with a larger effect size in HFpEF compared with HFrEF.[5] Other studies were also demonstrated that WRF is associated with an increased risk of cardiovascular death or HF hospitalization in patients with HFpEF.[40,41] Similar to these important studies, in our study, LOS was longer, the all-cause in-hospital mortality rate was significantly higher in patients with WRF than in patients without WRF (20% vs. 0%, respectively), and the 1-year all-cause mortality rate was found to be 38.6%. In addition, the long-term prognosis was poor in patients with WRF, and during the median 683 days of follow-up, all-cause postdischarge mortality was higher in the WRF group.

Study limitations

There are several limitations associated with the present study. This study has a retrospective design and represents the retrospective analysis of patients examined and treated by the study investigators. This situation may have introduced patient selection bias. The present study is a single-center study, and a few patients with HFpEF are included. Thus, the study population may not represent the general population. In our study, WRF is defined as an increase of ≥ 0.3 mg/dL in the serum creatinine level compared with the value on admission. However, this widely used definition of WRF has some limits, and the presence of WRF does not always indicate the deterioration of filtration capacity and kidney function.

Moreover, in the setting of ADHF, the baseline creatinine value on admission may not reflect the patient's actual creatinine value because of the presence of a possible cardiorenal syndrome. Therefore, some ADHF patients with WRF may have been missed. Because of these several limitations, the results of this study have to be interpreted carefully.

Conclusion

WRF was present in 37.7% of ADHF patients with preserved ejection fraction in the present study. Higher baseline creatinine and higher baseline NT-proBNP levels and Δ-CRP levels

during the first 48 h of hospitalization were associated with the development of WRF. Baseline creatinine levels and increased inflammatory status expressed by Δ−CRP were the independent predictors of WRF. Increased inflammatory status expressed by Δ−CRP is found to be a novel finding for predicting the development of WRF in patients with AD HFpEF. The presence of WRF during the first 5 days of hospitalization was found to be associated with a poorer prognosis, including longer LOS, higher all-cause in-hospital, and all-cause postdischarge mortality.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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