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ORIGINAL ARTICLE

Implications of worsening renal function before hospitalization for acute heart failure

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Abstract

Aims Kidney function changes dynamically during AHF treatment, but risk factors for and consequences of worsening renal function (WRF) at hospital admission are uncertain. We aimed to determine the significance of WRF at admission for acute heart failure (AHF).

Methods and results We evaluated a subgroup of 406 patients from The Acute Kidney Injury Neutrophil gelatinase–associated lipocalin Evaluation of Symptomatic heart failure Study (AKINESIS) who had serum creatinine measurements available within 3 months before and at the time of admission. Admission WRF was primarily defined as a 0.3 mg/dL or 50% creatinine increase from preadmission. Alternative definitions evaluated were a ≥0.5 mg/dL creatinine increase, ≥25% glomerular filtration rate decrease, and an overall change in creatinine. Predictors of admission WRF were evaluated. Outcomes evaluated were length of hospitalization, a composite of adverse in-hospital events, and the composite of death or HF readmission at 30, 90, and 365 days. Biomarkers' prognostic ability for these outcomes were evaluated in patients with admission WRF. One-hundred six patients (26%) had admission WRF. These patients had features of more severe AHF with lower blood pressure, higher BUN, and lower serum sodium concentrations at admission. Higher BNP (odds ratio [OR] per doubling 1.16–1.28, 95% confidence interval [CI] 1.00–1.55) and lower diastolic blood pressure (OR 0.97–0.98, 95% CI 0.96–0.99) were associated with a higher odds for the three definitions of admission WRF. The primary WRF definition was not associated with a longer hospitalization, but alternative WRF definitions were (1.3 to 1.6 days longer, 95% CI 1.0–2.2). WRF across definitions was not associated with a higher odds of adverse in-hospital events or a higher risk of death or HF readmission. In the subset of patients with WRF, biomarkers were not prognostic for any outcome.

Conclusions Admission WRF is common in AHF patients and is associated with an increased length of hospitalization, but not adverse in-hospital events, death, or HF readmission. Among those with admission WRF, biomarkers did not risk stratify for adverse events.

Keywords Acute heart failure; Acute kidney injury; Biomarkers; Cardiorenal syndrome

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Introduction

Kidney function can change dynamically during a hospitalization for acute heart failure (AHF) and the clinical significance of this change often depends on whether the patient remains congested or not.[1–4] Approximately 10 to 30% of patients with AHF have an improvement in renal function during hospitalization.[3] This improvement is thought to be from a reduction in high renal venous pressure that caused worsening renal function (WRF) prior to admission.[3,5] However, the correlation between increased renal venous pressure and a rise in serum creatinine is only present for some AHF patients.[6,7] This suggests the profile for AHF patients whose creatinine rises with congestion may be distinct from those whose kidney function does not change. Furthermore, some prior studies suggest that WRF present at the time of admission with AHF is associated with an increased risk of mortality and HF readmission.[8–10]

The Acute Kidney Injury Neutrophil gelatinase–associated lipocalin Evaluation of Symptomatic heart failure Study (AKINESIS) is a prospective, international, multicentre cohort study of AHF patients performed to better understand cardiorenal interactions.[2,11] In the current analysis, we aimed to determine if the profile and outcomes of patients with admission WRF were distinct from patients without WRF and if biomarkers could discriminate outcomes in patients with admission WRF.

Methods

The methods of AKINESIS have been previously described.[11] Briefly, patients were enrolled from January 2011 to September 2013 if they had findings consistent with AHF and had received or planned intravenous diuretic therapy. Exclusion criteria were (1) acute coronary syndrome, (2) dialysis-dependence or planned initiation during the hospitalization, (3) organ transplantation, (4) enrolment in a drug treatment study within the past 30 days or prior enrolment in this study, and (5) pregnant or a vulnerable population as determined by the institutional review board (IRB). The study was approved by IRBs at each study site and each patient signed informed consent. Of the original 927 patients, 411 patients had preadmission creatinine available within 3 months of presentation and 5 lacked admission creatinine leaving 406 patients as the analytic sample for this study. Comparison in baseline characteristics between included and excluded patients is shown in *Table S1*. Patients included in this analysis were enrolled during the same time frame of January 2011 to September 2013 but had higher co-morbidity than the excluded cohort, with higher prevalence of hypertension, diabetes, coronary artery disease (CAD), higher use of medications, and lower mean estimated glomerular filtration rate (eGFR) at the time of enrolment.

Definitions of worsening renal function

The primary definition for admission WRF was an admission creatinine either ≥0.3 mg/dL or 1.5 times higher than the preadmission creatinine recorded within 3 months before presentation. This definition was selected to match the serum creatinine change criteria of KDIGO stage 1 acute kidney injury (AKI).[12] As a sensitivity analysis, we also evaluated WRF defined as either an admission creatinine ≥0.5 mg/dL higher, ≥1.0 mg/dL higher, or ≥100% higher than preadmission, and an eGFR ≥25% or ≥50% lower than preadmission. eGFR was calculated using the CKD-EPI creatinine equation.[13] For these secondary definitions, we selected *a priori* to only evaluate definitions with ≥10% of patients experiencing admission WRF. Lastly, we evaluated delta creatinine (continuous creatinine change) defined as admission creatinine minus preadmission creatinine.

Outcomes

We evaluated which characteristics available at admission were associated with admission WRF. We evaluated if admission WRF was associated with the length of hospitalization and a composite of adverse in-hospital events defined as either admission to the intensive care unit (ICU), receiving inotropes, receiving positive pressure ventilation, renal replacement therapy (RRT) or death. Out of hospital events included a composite of all-cause mortality or HF readmission, all-cause mortality alone and HF readmission alone. These were assessed at 30 days, 90 days, and 1 year after enrolment.

Biomarker analysis

In patients meeting the primary admission WRF definition, we examined if the biomarkers urine neutrophil gelatinase-associated lipocalin (uNGAL), serum NGAL (sNGAL), B-type natriuretic peptide (BNP), high-sensitivity troponin I (hs-TnI) and galectin-3 measured at admission were associated with an adverse outcome. Details of these biomarker measurements have been previously published.[14]

Statistical analysis

Normally distributed continuous variables were expressed as means with standard deviations (SD), non-normally distributed variables were described as medians and interquartile ranges (IQR) and categorical variables were described as per-

centages. These were compared by Student's *t*-test, Mann–Whitney *U* test or χ^2 test comparing those with WRF versus non-WRF, as appropriate.

To determine which characteristics at time of hospital admission were associated with admission WRF, we built a multivariable logistic regression model using backward selection using a threshold *p*-value of <0.20, beginning with all variables in *Table 1* except those directly correlated with kidney function (creatinine, eGFR and BUN). We examined length of hospitalization using a time to event (discharge) analysis, adverse in-hospital events using logistic regression, and risk of out of hospital events using Cox proportional hazard models. We constructed models with sequential multivariable adjustment. Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for hypertension, diabetes, CAD, chronic obstructive pulmonary disease (COPD), systolic blood pressure (SBP), heart rate, and body mass index (BMI), preadmission eGFR, admission sodium, and admission haemoglobin. Finally, model 3 additionally adjusted for admission BNP. Variables were selected for clinical relevance and association with outcomes in prior AHF studies. Kaplan–Meier curves were constructed for out of hospital events with groups of non-WRF versus admission WRF with differences between groups compared by the log-rank test.

The associations of biomarkers with outcomes were assessed in the subset with the primary admission WRF definition. Only univariable analysis was performed given the smaller patient subgroups and fewer outcomes. Time to event, logistic regression and Cox proportional hazard models were performed as described above. Biomarkers with skewed distributions were evaluated after log base-2 transformed and described as 'per 2-fold higher'.

All analyses were performed using R version 4.0.3 (https://www.R-project.org/). A two-sided *P*-value of <0.05 was considered significant for all analyses unless otherwise specified.

Results

Baseline characteristics

Of the 406 patients included, 106 (26%) met the primary admission WRF definition. Of the alternative WRF definitions examined, ≥10% of patients had either a ≥0.5 mg/dL increase or ≥25% eGFR decrease, whereas <5% of patients met other definitions (Table S2). Patients experiencing the primary WRF definition were more often men, had higher BMI, and had higher preadmission creatinine but similar pre-admission eGFRs (*Table 1*). As expected, admission BUN and serum creatinine concentrations were higher. They also had lower admission SBP, diastolic blood pressure (DBP), and serum sodium concentrations compared with those without admission WRF.

Table 1 Baseline patient characteristics in those with and without WRF on admission

	No WRF (*n* = 300)	WRF (*n* = 106)	*P*-value
Age, years	68 (±13.3)	66.5 (±14.5)	0.10
Men	175 (58.3%)	74 (69.8%)	0.04
White	177 (59.0%)	64 (60.4%)	0.80
Enrolled at US site	203 (67.7%)	73 (68.9%)	0.82
BMI, kg/m^2	30.5 (±8.0)	32.7 (±8.9)	0.02
Hypertension	250 (83.3%)	96 (90.6%)	0.07
Hyperlipidaemia	173 (57.7%)	65 (61.3%)	0.51
Diabetes	141 (47.0%)	53 (50.0%)	0.60
Coronary artery disease	165 (55.0%)	60 (56.6%)	0.78
COPD	100 (33.3%)	35 (33.0%)	0.95
Tobacco use	54 (18.0%)	17 (16.0%)	0.65
ACE-I/ARB	189 (63.0%)	63 (59.4%)	0.52
Beta-blocker	232 (77.3%)	79 (74.5%)	0.56
Loop diuretics	234 (78%)	87 (82.1%)	0.38
NSAID	25 (8.3%)	6 (5.7%)	0.37
Systolic blood pressure, mmHg	138 (±27)	130 (±27)	<0.01
Diastolic blood pressure, mmHg	80 (±19)	73 (±15)	<0.01
Heart rate, b.p.m.	87 (±21)	86 (±24)	0.64
Haemoglobin, g/dL	11.3 (±2.4)	10.8 (±2.3)	0.07
Sodium, mEq/L	139 (±4)	137 (±6)	0.02
BUN, mg/dL	21 [16, 31]	35 [26, 56]	<0.01
BNP, pg/mL	534 [223, 1,141]	797 [278, 1309]	0.09
Pre-admission creatinine, mg/dL	1.10 [0.87, 1.41]	1.20 [0.89, 1.72]	0.04
Pre-admission eGFR, mL/min/1.73 m^2	66.8 (±26.7)	63.4 (±31.6)	0.28
Admission creatinine, mg/dL	1.12 [0.91, 1.48]	1.88 [1.39, 2.46]	<0.01
Admission eGFR, mL/min/1.73 m^2	64.3 (±25.5)	39.6 (±20.4)	<0.01

Note: Data presented as *N* (%), mean ± standard deviation or median [interquartile range].
Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; US, United States; WRF, worsening renal function.

Characteristics associated with admission WRF

A lower DBP and higher BNP were associated with a higher odds for all three WRF definitions (*Table 2*). Only male gender was also associated with a higher odds of the primary WRF definition. Higher BMI was associated with a higher odds of a ≥0.5 mg/dL creatinine increase and ≥25% decreased in eGFR, with similar albeit non-significant relationship for the primary WRF definition (*P*-value 0.053).

In-hospital outcomes

The median length of hospitalization was 5 [IQR 3 to 9] days. Patients with the primary WRF definition had a similar median length of hospitalization than those without WRF (median 5 [IQR 3 to 10] versus 5 [IQR 3 to 9] days, *P* = 0.22, *Table S3*). In the fully adjusted model (model 3), the primary WRF definition was not significantly associated with a longer length of hospitalization (*Figure 1A*, *Table S4*). However, admission WRF defined as ≥0.5 mg/dL increase in creatinine, a ≥25% eGFR decrease, or the change in creatinine from preadmission creatinine were all significantly associated with a longer length of hospitalization (*Figure 1A*).

There were 102 patients with at least one adverse in-hospital event. Counts for individual adverse events are higher than the composite as one patient could multiple adverse events. These include 5 received RRT, 44 received inotropes, 32 required positive pressure ventilation, 54 were admitted to the ICU and 12 died. More patients with WRF had an adverse event (36.8%) than those without WRF (21.0%, *Table S3*). In a model adjusted for all covariates except BNP, WRF was associated with an increased odds of adverse hospital events across definitions (*Table 3*). However, after further adjusting for BNP, all WRF definitions associations were attenuated and none remained significantly associated with adverse in-hospital events (*Figure 1B*, *Table 3*).

Death and HF readmission

The number of deaths or HF readmissions for those with and without admission WRF at 30 days, 90 days, and 1 year is shown in *Table S3*. At 1 year, 39% of patients with the primary WRF definition versus 37% without WRF experienced the composite of death or HF readmission composite outcome with no significant differences between the two groups (*Table S3*, *Figure 2*). The primary WRF definition was not associated with an increased risk of the composite outcome, death alone, or HF readmission alone at 30 days, 90 days and 1 year in univariable analysis or after multivariable adjustment (*Table 4*). Findings were similar when admission WRF was defined as ≥0.5 mg/dL increase in serum creatinine, ≥25% eGFR decrease, and change in serum creatinine on a continuous scale (*Tables S5–S7*).

Utility of biomarkers in patients with the primary admission WRF definition

Among the 106 patients who experienced admission WRF, none of the five biomarkers measured at the time of hospital admission were associated with length of hospitalization or adverse in-hospital events (*Table 5*). Most biomarkers were not associated with the composite outcome, death alone, or HF readmission alone at 30 days, 90 days, and 1 year (*Table 5*). Higher serum BNP was associated with an increased risk of the composite outcome at 90 days, and higher hs-TnI was associated with an increased risk of the composite outcome and death alone at 1 year, but these findings were not consistent across the different time points of follow-up. Notably, we hypothesized that higher serum or urine NGAL might differentiate the subset of WRF patients with intrinsic kidney injury from those with WRF from hemodynamic changes, and that these biomarkers may identify a subset of admission WRF patients at higher risk for adverse events. However, we did not observe that serum or urine concentrations of NGAL were as-

Table 2 Variables Associated with Admission Worsening Renal Function

WRF definition	≥0.3 mg/dL or 1.5 times creatinine increase		≥0.5 mg/dL creatinine increase		25% eGFR decrease	
Variable	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, per year	0.98 (0.96–1.00)	0.093			0.98 (0.96–1.00)	0.083
Male	1.88 (1.11–3.19)	0.020				
BMI, per mg/kg	1.03 (1.00–1.07)	0.053	1.04 (1.00–1.08)	0.038	1.04 (1.00–1.08)	0.027
Hypertension	2.00 (0.90–4.48)	0.090				
Diabetes					0.66 (0.39–1.12)	0.119
DBP, per mmHg	0.97 (0.96–0.99)	<0.001	0.98 (0.96–0.99)	0.011	0.97 (0.96–0.99)	0.001
Heart rate, per b.p.m.					1.01 (1.00–1.02)	0.058
Sodium, per mEq/L	0.96 (0.92–1.01)	0.122			0.95 (0.91–1.00)	0.056
BNP, per doubling	1.16 (1.00–1.34)	0.048	1.28 (1.05–1.55)	0.012	1.26 (1.08–1.47)	0.004

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; OR, odds ratio; WRF, worsening renal function.

Figure 1 Association between admission worsening renal definitions and length of stay and adverse in-hospital events in the fully adjusted multivariable model. All definitions of admission worsening renal function except the primary definition were associated with an increased length of stay in the fully adjusted model (A). None of the definitions of admission worsening renal function were associated with a higher odds of adverse in-hospital events in the fully adjusted model (B).

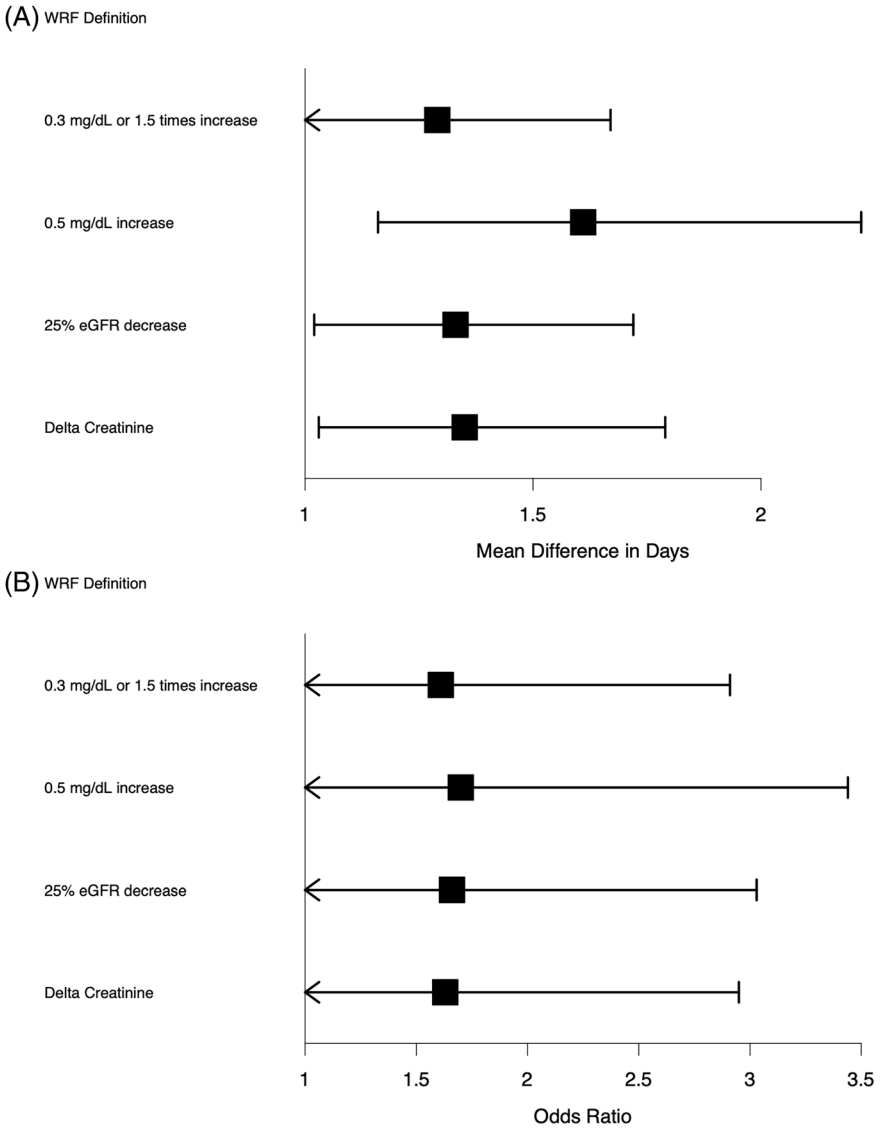

Table 3 Logistic regression for odds of adverse in-hospital events by WRF definition

WRF definition	Unadjusted OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
0.3 mg/dL or 1.5 times increase	2.2 (1.4–3.5)	1.7 (1.0–3.1)	1.6 (0.9–2.9)
0.5 mg/dL increase	2.3 (1.3–4.2)	1.9 (1.0–3.8)	1.7 (0.8–3.4)
25% eGFR decrease	2.0 (1.2–3.2)	1.9 (1.0–3.3)	1.7 (0.9–3.0)
Delta creatinine	2.4 (1.4–4.1)	1.9 (1.0–3.3)	1.6 (0.9–3.0)

Note: Model 1: age, sex, race. Model 2: Model 1 + hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, systolic blood pressure, heart rate, body mass index, eGFR before admission, admission sodium, admission haemoglobin. Model 3: Model 2 + BNP.
Abbreviations: CI, confidence interval; OR, odds ratio; WRF, worsening renal function.

Figure 2 Kaplan–Meier plots for death or heart failure readmission at 1 year by presence or absence of admission worsening renal function. Patients with admission worsening renal function (WRF) did not have significantly different (P = 0.55) rates of death or heart failure readmission at 1 year.

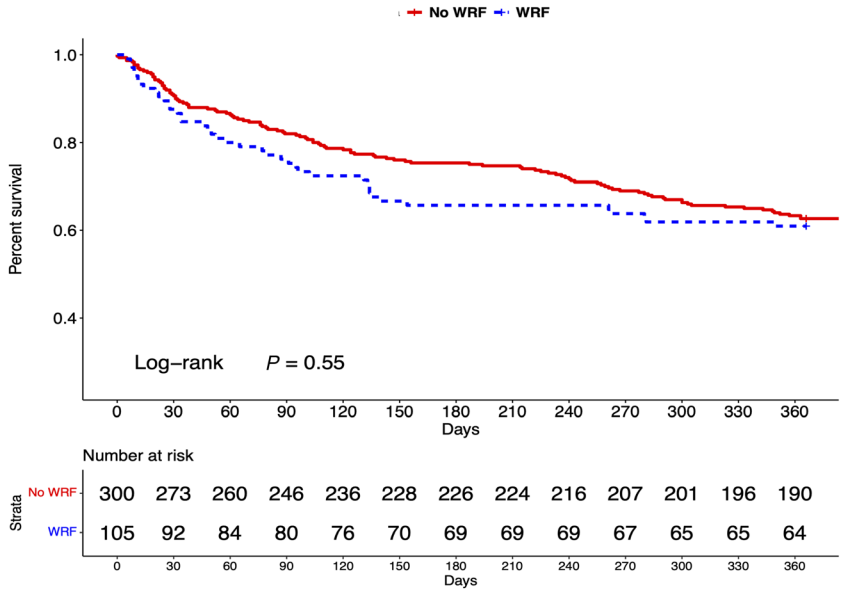

Table 4 Univariable and multivariable Cox models for out of hospital events by the WRF definition of creatinine increase of ≥0.3 mg/dL or ≥50% from preadmission

	Unadjusted HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Composite (n = events)			
30 days (n = 41)	1.36 (0.70–2.63)	1.09 (0.52–2.27)	1.04 (0.46–2.01)
90 days (n = 79)	1.38 (0.86–2.22)	1.19 (0.69–2.05)	1.06 (0.62–1.81)
1 year (n = 153)	1.12 (0.78–1.60)	0.92 (0.61–1.39)	0.89 (0.58–1.35)
Death (n = events)			
30 days (n = 19)	1.71 (0.67–4.34)	1.09 (0.33–3.66)	1.00 (0.30–3.37)
90 days (n = 35)	1.54 (0.76–3.09)	1.10 (0.48–2.54)	1.00 (0.44–2.27)
1 year (n = 83)	1.07 (0.66–1.75)	0.95 (0.54–1.69)	0.91 (0.51–1.61)
HF readmission (n = events)			
30 days (n = 23)	1.00 (0.39–2.54)	1.11 (0.41–2.98)	0.96 (0.36–2.59)
90 days (n = 48)	1.31 (0.71–2.41)	1.35 (0.69–2.64)	1.21 (0.62–2.37)
1 year (n = 84)	1.25 (0.78–1.99)	1.04 (0.62–1.75)	1.03 (0.61–1.74)

Note: Composite = death or HF readmission. Model 1: age, sex, race. Model 2: Model 1 + hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, systolic blood pressure, heart rate, body mass index, eGFR before admission, admission sodium, admission haemoglobin. Model 3: Model 2 + BNP.
Abbreviations: HF, heart failure; WRF, worsening renal function.

sociated with any of the in-hospital or out of hospital adverse outcomes among the admission WRF patients in this study.

Discussion

Considerable research has focused on the clinical significance of WRF during AHF hospitalizations, which may be influenced by the degree of diuresis, use of different medications, and the severity of AHF itself. Much less is known about the clinical significance of WRF at the time of presentation to the hospital with AHF. In this subgroup analysis of AKINESIS, we found that 26% of patients experienced WRF before presenting with AHF. These patients had features of more severe AHF with lower blood pressure, higher BUN, and lower serum sodium at the time of presentation. We found higher BNP and lower DBP were associated with higher odds of admission WRF. Although the primary WRF definition failed to reach statistical significance with length of hospitalization, a ≥0.5 mg/dL creatinine increase and ≥25% eGFR decrease were associated with this outcome. However, admission WRF was not associated with adverse in-hospital events nor with risk of death or HF hospitalization over 1 year. Lastly, among the subset of patients with WRF at the time of admission, the five biomarkers, including biomarkers of kid-

Table 5 Univariable analysis of biomarkers for outcomes in the 106 patients with the primary WRF definition

In-hospital outcomes	Serum NGAL	Urine NGAL	BNP	hs-TnI	Galectin-3
Length of hospitalization	**Days (95% CI)** 1.00 (0.85–1.16)	**Days (95% CI)** 1.04 (0.91–1.18)	**Days (95% CI)** 1.08 (0.96–1.21)	**Days (95% CI)** 1.08 (0.97–1.21)	**Days (95% CI)** 1.09 (0.79–1.48)
Adverse events (n = 39)	**OR (95% CI)** 1.19 (0.88–1.61)	**OR (95% CI)** 1.03 (0.84–1.27)	**OR (95% CI)** 1.18 (0.93–1.49)	**OR (95% CI)** 1.21 (0.95–1.54)	**OR (95% CI)** 1.36 (0.77–2.40)
Out of hospital outcomes	**Serum NGAL HR (95% CI)**	**Urine NGAL HR (95% CI)**	**BNP HR (95% CI)**	**Troponin HR (95% CI)**	**Galectin-3 HR (95% CI)**
Composite					
30 days (n = 13)	0.99 (0.66–1.49)	0.96 (0.73–1.26)	1.22 (0.86–1.72)	0.97 (0.69–1.37)	1.42 (0.70–2.88)
90 days (n = 25)	0.90 (0.68–1.21)	0.97 (0.80–1.18)	**1.42 (1.07–1.88)**	1.16 (0.92–1.46)	0.98 (0.59–1.71)
1 year (n = 41)	1.07 (0.85–1.34)	0.92 (0.80–1.07)	1.16 (0.97–1.40)	**1.21 (1.01–1.45)**	1.18 (0.78–1.79)
Death					
30 days (n = 7)	1.09 (0.62–1.92)	1.00 (0.69–1.45)	1.08 (0.70–1.65)	1.11 (0.73–1.71)	2.19 (0.94–5.10)
90 days (n = 12)	0.98 (0.64–1.50)	1.01 (0.76–1.35)	1.33 (0.90–1.97)	1.19 (0.86–1.64)	1.58 (0.78–3.22)
1 year (n = 22)	1.09 (0.80–1.49)	0.91 (0.74–1.11)	1.22 (0.94–1.60)	**1.28 (1.00–1.63)**	1.61 (0.96–2.70)
HF readmission					
30 days (n = 6)	0.89 (0.49–1.62)	0.90 (0.59–1.37)	1.46 (0.81–2.63)	0.81 (0.51–1.29)	0.67 (0.19–2.32)
90 days (n = 15)	0.82 (0.56–1.20)	0.89 (0.68–1.16)	1.38 (0.97–1.97)	1.05 (0.78–1.41)	0.47 (0.20–1.08)
1 year (n = 25)	1.02 (0.76–1.37)	0.87 (0.72–1.06)	1.07 (0.86–1.34)	1.03 (0.83–1.29)	0.82 (0.45–1.48)

Note: Bolded values have P-value <0.05.
Abbreviations: BNP, B-type natriuretic peptide; HF, heart failure; HR, hazard ratio; hs-TnI, high-sensitivity troponin I; NGAL, neutrophil gelatinase-associated lipocalin; OR, odds ratio; WRF, worsening renal function.

ney injury, largely did not identify individuals at higher risk for either in-hospital or long-term outcomes.

Single centre studies reported an increased risk of death and HF readmission among patients experiencing WRF at the time of admission with AHF; however, there are notable differences between these studies and ours.[8–10] One study found primarily stage 2 and 3 KDIGO AKI was associated with adverse events of death and HF readmission, but not stage 1.[9] This is similar to our findings, as the primary WRF definition captured stage 1 or greater KDIGO AKI and was not associated with outcomes, whereas more stringent criteria of WRF were associated with increased length of hospitalization. Another study only included AHF patients admitted to ICU and did not use preadmission creatinine to define admission WRF.[8] Conversely, Testani et al. found AHF patients with admission WRF and subsequent improvement in kidney function during the hospitalization only had an increased mortality when WRF recurred after discharge.[5] These prior studies all reported single centre experiences, whereas ours evaluated a multicentre study population. Thus, the variability in study findings may reflect the unique patient populations and treatment approaches at each centre. By evaluating a multicentre cohort from the United States and Europe, we reduced potential confounding of institutional practices and patient populations, and this may partially explain differences across studies.

Baseline kidney function in some patients presenting with AHF may be unknown and the presence of admission WRF can only be determined after kidney function improves during the hospitalization. Determining variables associated with admission WRF can help identify which patients are at their baseline level of kidney dysfunction versus those anticipated to have an improvement. We found higher BNP and lower DBP were associated with a higher odds of admission WRF. This fits with the current pathophysiologic understanding that WRF in AHF is largely a hemodynamic effect with lower DBP reflecting a lower perfusion pressure and higher BNP reflecting greater congestion.[2,3,15] This hemodynamic driver of admission WRF also fits with our other findings.

We found admission WRF was only associated with a longer length of hospitalization, but not adverse in-hospital events or long-term death and HF readmission. Interestingly, admission WRF was significantly associated with adverse in-hospital events until adjusting for BNP in the final model. This reinforces the importance of congestion status and AHF severity are more important drivers of outcomes than WRF.[16,17] Other potential unmeasured confounders and drivers of AHF outcomes may have further nullified admission WRF's association with outcomes.

AHF research has identified several useful prognostics biomarkers. For example, previous studies have clearly demonstrated that lower serum sodium, lower blood pressure, higher BUN and higher BNP are associated with short- and long-term adverse outcomes in AHF.[18–20] We hypothesized that presentation with WRF would similarly be associated

with these outcomes, but we failed to confirm that hypothesis here. This should provide clinicians some reassurance. Although patients with WRF at admission appeared to have signs of worse AHF overall, the deterioration of kidney function prior to admission was not in and of itself associated with adverse long-term outcomes. This is likely because admission WRF reflects hemodynamic consequence of worse AHF on the kidney and may not reflect intrinsic kidney injury per se in most patients. More important are the patient's and kidney's response to therapy for long-term prognosis.[2,3]

Although our findings support that most AHF patient's experience admission WRF from hemodynamic deterioration related to congestion, reduced kidney perfusion, or medications, there could be a subset of patients that has intrinsic kidney damage leading to reduced diuresis and fluid overload. We hypothesized that such individuals may have different hospital courses and long-term outcomes. Among the subset of 106 patients with WRF, and among the five biomarkers we evaluated, none were consistently associated with either in-hospital or out of hospital outcomes. This includes the two kidney tubular injury biomarkers (sNGAL and uNGAL). These findings align with other studies suggesting that tubule injury biomarkers are not uniformly prognostic of adverse outcomes in AHF patients.[11,21,22] However, the two tubular injury biomarkers measured (sNGAL and uNGAL) reflect similar kidney injury, just in different mediums (blood and urine), whereas there are other novel kidney injury and function biomarkers where relationships with outcomes could be different.[23] Because most admission WRF is likely due to hemodynamic changes, we may have been underpowered to detect a small subset of patients who experienced intrinsic kidney injury where relationships with outcomes may have differed. Future studies with larger numbers of patients with admission WRF patients will be needed to determine if such a subset can be identified, and re-investigate its significance for subsequent clinical events.

It is still unclear why in some patients with AHF kidney function deteriorates with congestion, whereas in others, it remains unchanged. Animal studies have shown increased renal venous pressure promotes neurohormonal activation and increased afferent arteriole resistance leading to reduced eGFR.[24–26] Similar physiologic changes may occur in AHF, but not in every patient as shown in our current analysis and prior studies. Thus, further research is needed to better understand these distinct AHF populations and determine when a cardiorenal versus renocardiac process leads to a change in kidney and cardiac function.

Strengths and limitations

Strengths of this study include its evaluation of a diverse multicentre international cohort. We also focused only on patients with a creatinine measurement available prior to admission rather than extrapolating WRF from other time points. Lastly, we explored multiple biomarkers for their prognostic significance in admission WRF.

Our study also has important limitations. The influence of identified and unidentified confounders cannot be excluded. Most patients in this study had normal kidney function or mild kidney dysfunction, thus findings cannot necessarily be extrapolated to patients with more advanced kidney disease. Serum creatinine measurements were only available within 3 months prior to admission which may not extend far enough to detect true baseline kidney function and the date of measurement was not available. We also do not know if medical therapy was altered between pre-hospital creatinine measurement and hospitalization. We lacked adequate echocardiographic information to determine if ejection fraction or other parameters may have facilitated explaining our findings. Lastly, clinicians were not blinded to creatinine values prior to admission, and they may have changed their treatment strategy in response to changes in kidney function; however, our data reflect real-world experiences in AHF management and prior studies similarly did not blind clinicians to preadmission creatinine.

Conclusions

Presentation to the hospital with WRF is common in patients presenting with AHF. Higher BNP and lower DBP at admission are associated with an increased odds of admission WRF, consistent with hemodynamic perturbations driving most cases of WRF in this setting. Although admission WRF was associated with a longer hospitalization, it was not associated with adverse in-hospital events or long-term risk of death or HF readmission. Additionally, among the subset with admission WRF, the five biomarkers measured at admission did not consistently discriminate which patients with admission WRF were at greatest risk for adverse events. Further research is needed to better understand the cardiorenal interactions of AHF patients who experience WRF with congestion.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of Included and Excluded Participants.
Table S2. Number Patients with Admission WRF by Different Definitions.
Table S3. Outcomes by admission WRF versus no WRF.
Table S4. Time to Event Analysis for Difference in Mean Length of Hospitalization by WRF Definition.
Table S5. Univariable and Multivariable Cox Models for Out of Hospital Events with WRF Defined as 0.5 mg/dL Increase.
Table S6. Univariable and Multivariable Cox Models for Out of Hospital Events with WRF Defined as 25% eGFR Decrease.
Table S7. Univariable and Multivariable Cox Models for Out of Hospital Events by Delta Creatinine.

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