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Incidence, Predictors at Admission, and Impact of Worsening Renal Function Among Patients Hospitalized With Heart Failure

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OBJECTIVES The goal of this study was to determine the prevalence of worsening renal function (WRF) among hospitalized heart failure (HF) patients, clinical predictors of WRF, and hospital outcomes associated with WRF.

BACKGROUND Impaired renal function is associated with poor outcomes among chronic HF patients.

METHODS Chart reviews were performed on 1,004 consecutive patients admitted for a primary diagnosis of HF from 11 geographically diverse hospitals. Cox regression model analysis was used to identify independent predictors for WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 μmol/l). Bivariate analysis was used to determine associations of development of WRF with outcomes (in-hospital death, in-hospital complications, and length of stay).

RESULTS Among 1,004 HF patients studied, WRF developed in 27%. In the majority of cases, WRF occurred within three days of admission. History of HF or diabetes mellitus, admission creatinine ≥1.5 mg/dl (132.6 μmol/l), and systolic blood pressure >160 mm Hg were independently associated with higher risk of WRF. A point score based on these characteristics and their relative risk ratios predicted those at risk for WRF. Hospital deaths (adjusted risk ratio [ARR] 7.5; 95% confidence intervals [CI] 2.9, 19.3), complications (ARR 2.1; CI 1.5, 3.0), and length of hospitalizations >10 days (ARR 3.2, CI 2.2, 4.9) were greater among patients with WRF.

CONCLUSIONS Worsening renal function occurs frequently among hospitalized HF patients and is associated with significantly worse outcomes. Clinical characteristics available at hospital admission can be used to identify patients at increased risk for developing WRF. (J Am Coll Cardiol 2004; 43:61–7) © 2004 by the American College of Cardiology Foundation

Several studies of patients with heart failure (HF) have reported an association between impaired renal function and unfavorable outcomes (1–8). The change in renal function during hospitalization for HF may also have prognostic importance. Krumholz et al. (9), in a study of Medicare beneficiaries with HF, demonstrated that worsened renal function (WRF), defined as a rise in serum creatinine of >0.3 mg/dl (26.5 μmol/l) during hospitalization, occurred frequently (28% incidence) and was associated with specific clinical characteristics present upon admission. In addition, patients with WRF had longer lengths of stay, higher in-hospital costs, increased in-hospital mortality, and greater likelihood of readmission. However, that study included only Medicare patients and needs to be validated in a general HF population. Therefore, we designed a multicenter investigation to determine the frequency and timing, as well as the predictors, of WRF among a broad population of patients with HF. We also sought to identify those at greatest risk for developing WRF during their hospitalizations based on admission clinical characteristics.

METHODS

Data source. We obtained inpatient medical records for a geographically diverse sample of HF patients hospitalized between July 1, 1997, and June 30, 1998, at 11 academic medical centers. The participating sites were Rhode Island Hospital, Yale-New Haven Hospital, Duke University Medical Center, Hospital of the University of Pennsylvania, University of Cincinnati Medical Center, Brigham and Women's Hospital, University Health Center-University of Maryland, San Francisco Veterans Affairs Medical Center,

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Abbreviations and Acronyms

AF = atrial fibrillation
BP = blood pressure
BUN = blood urea nitrogen
EF = ejection fraction
HF = heart failure
LV = left ventricular
WRF = worsening renal function

Barnes Jewish Hospital, Vanderbilt University Medical Center, and The Cleveland Clinic Foundation. Consecutive HF hospitalizations were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) principal discharge diagnoses codes 428.0, 428.1, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93.

Four nurses experienced in critical care or emergency care and affiliated with an independent contract research organization abstracted data from medical records. To verify the accuracy of chart abstraction, an independent nurse abstractor re-evaluated information in four categories (creatinine, inclusion and exclusion criteria, and discharge dates) in 55 charts (15 charts for each of three abstractors and 10 for the fourth). Discrepancies between the original abstractions and these reassessments were <0.4% and were all corrected. Creatinine values for all 1,004 patients in the final study population were checked, and no discrepancies were detected. In addition, comprehensive examinations of all data fields were completed in a subset of 10% of the subjects. Less than 0.5% discrepancy was detected.

The abstractors confirmed the diagnosis of HF in this group by documenting at least one symptom and at least one sign of HF. Symptoms included new onset or worsening shortness of breath (dyspnea at rest or with exertion, orthopnea, paroxysmal nocturnal dyspnea, cough/nocturnal cough) or nonspecific symptoms that may be manifestations of HF (fatigue, confusion/disorientation). Signs included increased jugular venous pressure, S3 gallop, bilateral pulmonary rales or crackles (more than basilar), hypotension/cardiogenic shock, cardiac arrest, respiratory rate >24, peripheral edema, increased weight from baseline, or radiologic signs (pulmonary edema, cephalization of pulmonary vessels, pleural fluid, interstitial edema, alveolar fluid/edema, or cardiomegaly).

Exclusion criteria were designed to assemble a population of typical adult HF patients. Patients were excluded if their hospitalizations were for an elective procedure (e.g., percutaneous transluminal coronary angioplasty, pacemaker, or cardioversion) or if their hospital length of stay was <2 days. Other exclusion criteria included severe aortic stenosis, anticipated cardiac transplantation, transfer from another in-hospital setting, chronic dialysis, use of a left ventricular (LV) assist device, high-output HF, age <20 years, concomitant use of an investigational product or device, and patients receiving chemotherapy. Subjects were also excluded if creatinine values were not documented at admission.

Outcomes and candidate predictors associated with WRF. The principal outcome was WRF, defined as an increase in serum creatinine of >0.3 mg/dl (26.5 μmol/l) from admission, consistent with several previous investigations (9–11).

Baseline clinical variables included subjects' demographic characteristics, past medical histories, medications on admission, and symptoms and physical signs on presentation. In analyses to determine the prognostic importance of WRF, the outcome measures were hospital length of stay, in-hospital mortality, and complications occurring after the rise in creatinine. Complications were defined as shock, myocardial infarction, stroke, major infection/sepsis, clinically significant hypotension, and new onset atrial fibrillation (AF) with ventricular rates >100 beats/min.

Statistical analysis. Chi-square analyses were used to compare incidence of WRF between different recruitment sites. A Kaplan-Meier plot of freedom from WRF was constructed to show the process of WRF development. In bivariate analyses, the associations between patients' characteristics and the development of WRF were assessed.

Independent predictors of WRF were identified using multivariable Cox regression models with stepwise selection method. Time to WRF was the outcome with censoring at the time of hospital discharge for those without an increase in creatinine. Variables were entered at an entry level of significance $p < 0.1$ and kept in the model at an exit significance level $p < 0.05$. To confirm that our model is stable, we used bootstrap analysis method (12). We bootstrapped the original data 1,000 times to get 1,000 samples; each bootstrapping sample was the same size, each was randomly selected from the original data, and each was selected independently, that is, with the chance that records could be selected more than once. For each bootstrapping sample, we repeated our model and determined the coefficients. We could, thereby, generate summary analysis for the 1,000 models and determine variation of the coefficients. By showing only a small variation of coefficients, we concluded that the model was stable. A risk score was calculated as the arithmetic sum of point values assigned to each independent predictor based on the multivariate-adjusted risk relationship in the final Cox model, that is, proportionate to the hazard ratio. The relationship between this risk score and WRF was evaluated using the Cochran-Armitage (13) trend test to assess significance of the trend.

Associations of the development of WRF with patients' outcomes (length of stay >10 days, complications, and in-hospital mortality) were assessed through bivariate analysis. The analysis was repeated on subgroups stratified by age (20 to 59 years, 60 to 79 years, ≥80 years), gender, and baseline creatinine (creatinine <1.0 mg/dl [88.4 μmol/l], 1.0 [88.4 μmol/l] ≤ creatinine <1.5 mg/dl [132.6 μmol/l], 1.5 mg/dl [132.6 μmol/l] ≤ creatinine <2.5 mg/dl [221.0 μmol/l]; creatinine ≥2.5 mg/dl [221.0 μmol/l]). The association of WRF with patients' outcomes was assessed by

logistic regression analysis adjusting for potential confounding factors, such as: significant predictors of WRF, as well as age, race, history of AF, cerebral vascular accident, HF, diabetes mellitus, previous use of digoxin, symptoms of othopnea, presentation of hypotension (i.e., blood pressure [BP] <90 mm Hg with associated symptoms), edema, high respiratory rate, systolic BP more than 160 mm Hg, laboratory values of potassium, creatinine, and blood urea nitrogen (BUN). Odds ratios and their 95% confidence intervals were transferred into risk ratios, and the corresponding confidence intervals (14).

Variables missing from more than 15% of the study population were excluded from consideration. These variables were oxygen saturation (30%), gamma-glutamyltranspeptidase (94%), aspartate aminotransferase (36%), alanine aminotransferase (64%), and bilirubin (48%). Continuous variables, dichotomized or categorized based on clinical significance as shown in the tables, were age, systolic BP, pulse, respiratory rate, sodium, potassium, creatinine, BUN, and hematocrit. Missing categorical data elements were assumed to be "not present" for the variable, and a separate dummy indicator was used if more than 5% of the values were missing, as was the case for smoking status (8%) and LV ejection fraction (EF) (10.5%).

The study was funded by Biogen, Inc., Cambridge, Massachusetts; decisions regarding the study design, collection, analysis, and interpretation of the data, and the approval of the finished manuscript for publication were at the full discretion of the authors. All analyses were performed using PC-SAS version 8.0 (SAS Institute, Inc., Cary, North Carolina) and STATA version 6.0 (Stata Corp., College Station, Texas).

RESULTS

Study population. Charts from 1,009 patients were abstracted. Five of these charts were excluded from analysis because they were missing admission creatinine levels. The remaining 1,004 patients constituted our study sample.

Patient characteristics. Patient baseline characteristics are listed in Table 1. Mean age (±SD) of the study population was 67 ± 15 years with 18% of the cohort >80 years of age. Nearly half the total population was female, and 54% were white. Mean EF was 34.2% among the 899 of 1,004 subjects (89.5%) whose EFs were measured. Left ventricular EF values measured >55% among 21% of the subjects whose EFs were measured.

Admission symptoms and signs are listed in Table 2. At presentation, most of the study population complained of dyspnea, and two-thirds had peripheral edema. The prevalence of baseline severe renal insufficiency was relatively low (baseline creatinine >2.5 mg/dl [221.0 μmol/l] in 11% and >4.0 mg/dl [353.6 μmol/l] in 3% of the subjects).

Incidence of WRF. Worsening renal function occurred in 273 patients (27%) (Fig. 1). The incidence of WRF was similar across the 11 recruitment sites, and its onset occurred within the first three hospital days in 142 of the 273 patients (52%).

Risk factor stratification based on medical history and hospital presentation. Table 3 indicates independent risk factors for WRF. A history of HF, pharmacologically treated diabetes mellitus, admission creatinine, and elevated systolic BP (>160 mm Hg) were the factors most strongly associated with WRF. In addition, admission creatinine (≥1.5 mg/dl [132.6 μmol/l]) <2.5 mg/dl (221 μmol/l) as well as ≥2.5 mg/dl (221.0 μmol/l) were associated with incremental risk compared with admission creatinine ≤1.5 mg/dl (132.6 μmol/l). The bias of coefficients of these factors is negligible (rounds to 0), and bootstrap analysis with 1,000 replicas demonstrates that the model is stable.

A risk score for WRF was devised based on the risk factors. Points were assigned to each risk factor listed in Table 3 based on the respective relative risk ratios. One point was assigned to history of HF, history of diabetes mellitus, and systolic BP >160 mm Hg at admission. Two points were assigned to creatinine 1.5 (132.6 μmol/l) to 2.4 mg/dl (212.16 μmol/l), and three points were assigned to creatinine ≥2.5 mg/dl (221 μmol/l). Table 4 shows the relationship between risk score and WRF. Patients with higher point totals were more likely to develop WRF. The 22% of the total sample with a risk score of ≥4 had a 53% likelihood of developing WRF compared with only a 10% risk among the 12% of the population with a risk score of 0 ($p < 0.001$ for the trend). Relative to the group of patients with a risk score of 0, both the groups of patients with scores 1 and 2 had approximately twice the likelihood of developing WRF (see "relative risk" column in Table 4). Compared with those with risk score of 0, the group with risk score 3 had approximately triple the risk of developing WRF. The group with risk score 4 had >5 times the risk.

WRF and outcomes. Logistic regression analysis shows that clinical outcomes were significantly worse among subjects with WRF. Risk ratios for death during hospitalization, complications, and length of stay >10 days increased sevenfold, twofold, and threefold, respectively, in comparisons of those who developed WRF with those who did not. After adjusting for potential confounding factors including demographics (age, race), medical history (AF, cerebrovascular accident, HF, diabetes, use of digoxin), admission characteristics (othopnea, hypotension, edema, high respiratory rate, systolic BP more than 160 mm Hg), and lab values (potassium, creatinine, and BUN), associations between WRF and worse clinical outcomes remained significant. Results were consistent among subgroups defined by strata of age, gender, and baseline creatinine.

DISCUSSION

The present study adds to the growing evidence that WRF is common among patients hospitalized for HF and is associated with markedly poorer outcomes. The principal findings are: 1) 27% of patients develop WRF, as defined by

Table 1. Baseline Characteristics of Heart Failure Patients and WRF

	Total (1,004)		WRF				
			No (731)		Yes (273)		
	#	%	#	%	#	%	p Value
Demographics							
Age: mean (SD)	67.3	14.6	66.8	15.0	68.7	13.4	0.07
Age >80	182	18.1	133	18.2	49	17.9	0.93
Female	490	48.8	359	49.1	131	48.0	0.75
White	538	53.6	390	53.4	148	54.2	0.81
Smoker	235	23.4	178	24.4	57	20.9	0.25
Ejection fraction							0.33
Normal (LVEF ≥55)	212	21.1	154	21.1	58	21.2	0.95
Mild LV dysfunction (55 > LVEF ≥ 40)	164	16.3	114	15.6	50	18.3	0.30
Moderate LV dysfunction (40 > LVEF ≥ 20)	392	39.0	279	38.2	113	41.4	0.35
Severe LV dysfunction (20 > LVEF ≥ 0)	131	13.0	102	14.0	29	10.6	0.16
Missing assessment of LVEF	105	10.5	82	11.2	23	8.4	0.20
Medical history							
Prior heart failure	636	63.3	444	60.7	192	70.3	0.0050*
Prior renal failure	230	22.9	120	16.4	110	40.3	<0.0001*
Hypertension	703	70.0	503	68.8	200	73.3	0.17
Atrial fibrillation	237	23.6	170	23.3	67	24.5	0.67
Noninsulin-dependent diabetes	206	20.5	139	19.0	67	24.5	0.05
Insulin-dependent diabetes	204	20.3	133	18.2	71	26.0	0.0062*
Stroke	155	15.4	98	13.4	57	20.9	0.0035*
Peripheral vascular diesease	128	12.7	80	10.9	48	17.6	0.0050*
Angina	360	35.9	252	34.5	108	39.6	0.14
Myocardial infarction	302	30.1	213	29.1	89	32.6	0.29
Prior medications							
Prior ACE-I	473	47.1	335	45.8	138	50.5	0.18
Prior ARBs	52	5.2	39	5.3	13	4.8	0.72
Prior BB	224	22.3	154	21.1	70	25.6	0.12
Prior CCB	258	25.7	166	22.7	92	33.7	0.0004
Prior vasodilators	337	33.6	226	30.9	111	40.7	0.0036*
Nitrates	287	28.6	191	26.1	96	35.2	0.0048*
Hydralazine	48	4.8	26	3.6	22	8.1	0.0029*
Others	57	5.7	39	5.3	18	6.6	0.44
Prior diuretics	703	70.0	508	69.5	195	71.4	0.55
Prior ASA	230	22.9	153	20.9	77	28.2	0.0147*
Prior NSAID	63	6.3	49	6.7	14	5.1	0.36
Prior digoxin	371	37.0	278	38.0	93	34.1	0.25

*$p < 0.05$.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = aspirin; BB = beta-blocker; CCB = calcium channel blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; WRF = worsening renal function.

serum creatinine increase >0.3 mg/dl (26.5 μmol/l), a previously identified threshold associated with worse outcomes; 2) several baseline characteristics are associated with the development of WRF, and a score derived by weighting these variables is highly predictive; and 3) in a diverse group of consecutive patients, WRF remains a powerful predictor of increased risk of death, increased complications, and prolonged hospitalizations.

The risk associated with post-admission WRF was first reported in a study limited to older HF patients (mean age 79 ± 8 years; 44% age over 80 years) that showed a similarly high incidence of WRF (28%) (9). Both the previous and the present studies demonstrate that WRF occurs early, appearing within seven days of hospitalization in 90% of cases and 81% of cases, respectively (data not shown). The early occurrence of WRF in the course of hospitalizations for decompensated HF suggests that renal deterioration is related to inherent mechanisms of disease or to the impact of therapy administered upon admission, rather than to progressively worsening clinical status over prolonged hospitalization.

The mechanisms responsible for WRF are complex and not well-defined. Intuitively, hemodynamic abnormalities, such as hypotension or low cardiac output, might be expected to play a role (15). However, hypotension was uncommon in this population, and, in fact, it was hypertension that emerged as a predictor of WRF. Similarly, intravascular hypovolemia can cause WRF, but our data indicated that WRF was more likely in patients with elevated jugular venous pressure at admission. Still, corroborating hemodynamic measurements were rarely available. It is noteworthy that EF was not a predictor of WRF and that, among patient subgroups with mild, moderate, and severe LV systolic impairment as well as those with normal

Table 2. Presenting Symptoms and Signs of Heart Failure Patients and WRF

	Total (1,004)		WRF				
			No (731)		Yes (273)		
	#	%	#	%	#	%	p Value
Symptoms upon hospitalization for heart failure							
Dypnea at rest or on exertion	960	95.6	696	95.2	264	96.7	0.30
Othopnea	592	59.0	428	58.5	164	60.1	0.66
Paroxysmal nocturnal dyspnea	399	39.7	287	39.3	112	41.0	0.61
Fatigue	257	25.6	201	27.5	56	20.5	0.0241*
Confusion/disorientation	52	5.2	41	5.6	11	4.0	0.32
Signs on presentation							
S3 gallop	263	26.2	185	25.3	78	28.6	0.30
Increased jugular venous pressure	543	54.1	376	51.4	167	61.2	0.0059*
Bilateral rales or crackles > basilar	456	45.4	325	44.5	131	48.0	0.32
Peripheral edema	694	69.1	504	68.9	190	69.6	0.84
Hypotension (SBP <90, with symptoms)	25	2.5	17	2.3	8	2.9	0.58
Hypertension (SBP >160)	322	32.1	217	29.7	105	38.5	0.0080*
Pulse ≥100 beats/min	383	38.1	292	39.9	91	33.3	0.06
Respiratory rate ≥24 beats/min	499	49.7	351	48.0	148	54.2	0.08
Atrial fibillation	190	18.9	145	19.8	45	16.5	0.23
CHF/pulmonary edema on CXR	773	77.0	555	75.9	218	79.9	0.19
Laboratory results							
Sodium >145	23	2.3	14	1.9	9	3.3	0.19
Sodium <135	142	14.1	104	14.2	38	13.9	0.90
Potassium >5	96	9.6	62	8.5	34	12.5	0.06
1.5 ≤ creatinine <2.5	247	24.6	155	21.2	92	33.7	<0.0001*
Creatinine ≥2.5	112	11.2	50	6.8	62	22.7	<0.0001*
BUN >50	116	11.6	63	8.6	53	19.4	<0.0001*
Hematocrit <30	128	12.7	83	11.4	45	16.5	0.0301*

BUN = blood urea nitrogen; CHF = congestive heart failure; CXR = chest X-ray; SBP = systolic blood pressure; WRF = worsening renal function.

LVEFs, proportions of patients who developed WRF were similar. These findings are consistent with those of Weinfeld et al. (16) who showed no correlation between renal deterioration and cardiac output, filling pressures, or baseline systemic vascular resistance in a study of 48 HF patients. It seems likely that other endogenous vascular factors, including endothelin, nitric oxide, prostaglandin, natriuretic peptides, and vasopeptidase inhibitors may affect renal perfusion independently of central hemodynamics (17,18). Comorbid conditions or the treatments utilized may also play a critical role in the development of WRF.

In addition, although HF patients with elevated creatinine levels at hospital admission were especially likely to develop WRF, it was remarkable that increases in creatinine >0.3 mg/dl (26.5 μmol/l) were clinically consequential in all subgroups of subjects, regardless of baseline or peak

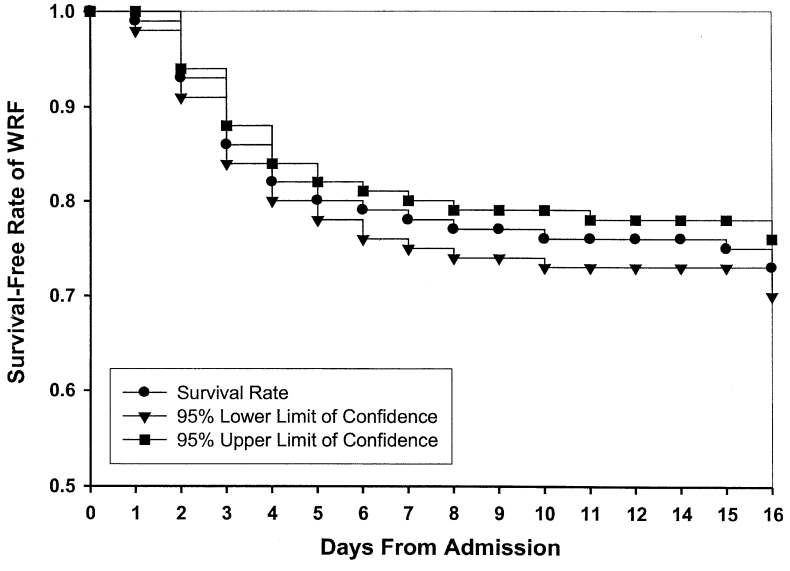

Figure 1. Time without worsening renal function during heart failure hospitalizations. WRF = worsening renal function.

Table 3. Risk Factors for WRF*

Description	Parameter Estimate	Hazard Ratio	Confidence Interval†		Weight	Bootstrap Results‡ (1,000 Replicas)		
			Lower	Upper		Bias	Lower	Upper
History of prior CHF	0.2715	1.312	1.008	1.707	1	0.0048	0.0061	0.5368
Diabetes	0.3375	1.401	1.102	1.783	1	−0.0022	0.1007	0.5744
SBP >160	0.3108	1.365	1.064	1.749	1	−0.0004	0.0624	0.5592
1.5 ≤ creatinine < 2.5	0.7408	2.098	1.595	2.760	2	−0.0029	0.4914	0.9903
Creatinine ≥2.5	1.2448	3.472	2.537	4.752	3	0.0047	0.9315	1.5581

*Cox regression with stepwise method using baseline as candidate variables; †95% confidence interval of hazard ratio; ‡ Only bias from the original parameter estimate and 95% confidence interval of the original parameter estimates were reported.
CHF = congestive heart failure; SBP = systolic blood pressure; WRF = worsening renal failure.

serum creatinine level. In fact, when change in creatinine is expressed as a percentage, the >0.3 mg/dl increase among those with high baseline serum creatinine was relatively smaller than the percent creatinine change among those with low baseline serum creatinine, and yet all manifest similar untoward outcomes.

Multivariable analysis identified four clinical parameters present at admission (history of pre-existing HF, diabetes mellitus, admission creatinine of ≥1.5 mg/dl [132.6 μmol/l], admission systolic BP >160 mm Hg) that are strongly and independently associated with WRF. Notably, age was not associated with WRF in this study population, indicating that age-related systemic effects are not specifically related to the onset of WRF. A simple score based on these admission variables distinguished risks of developing WRF ranging from 10% to 53% among different HF patients.

Although it is recognized that renal function may be more accurately assessed using calculated creatinine clearance, it is also relevant that 24-h urine collection is more cumbersome and costly and lends itself less readily to serial measurement. A strength of this investigation is that the simpler and more readily available measurement of serum creatinine provides a powerful tool for predicting adverse outcomes. The previous report by Weinfeld et al. (16) studying renal function and HF highlights these methodological differences. Those investigators used creatinine clearance rates as well as serum creatinine to assess renal performance among HF patients. Patients with reduced creatinine clearance rates were more likely to develop aggravated renal deterioration and poor outcomes despite similar baseline creatinine level. Nonetheless, our study provides firm support for using increases in serum creatinine to predict adverse outcomes regardless of "actual" renal function. Furthermore, serum creatinine levels are less expensive than assessments of creatinine clearance, and they are more clinically useful for monitoring short-term fluctuations in renal function.

Table 4. Risk Score and WRF

Score	#	%	WRF		Relative Risk
			#	%	
0	123	12.25	12	9.76	1 (Reference)
1	257	25.60	48	18.68	1.91
2	251	25.00	51	20.32	2.08
3	155	15.44	47	30.32	3.11
4+	218	21.71	115	52.75	5.40
Cochran-Armiage trend test (p value)				<0.001	
Total	1,004	100	273	27.19	

Score for "1.5 ≤ creatinine <2.5" is 2 and for "creatinine ≥2.5" is 3.
WRF = worsening renal function.

Whether 0.3 mg/dl (26.5 μmol/l) increases in serum creatinine is the best gradation of renal deterioration is also controversial. Some investigators have used a rise in serum creatinine above a threshold to define renal insufficiency (e.g., creatinine >2.5 mg/dl [221.0 μmol/l]) or a percentage increase from baseline (e.g., >25% increase), or a combination of these factors (15). In the current investigation, we utilized a predetermined definition of an increase in creatinine >0.3 mg/dl from admission based on observations in prior studies (9–11). Notably, this definition of WRF enables us to show that WRF is associated with adverse outcomes even in subjects whose peak serum creatinine was <2.5 mg/dl (221.0 μmol/l). Other definitions of WRF are compared in a related analysis by Gottlieb et al. (19) who demonstrate that any detectable change in serum creatinine, regardless of peak creatinine, is associated with increased mortality and prolonged hospital stay. Using a threshold of 0.3 mg/dl creatinine, the sensitivity and specificity of WRF were 81% and 62%, respectively, for in-hospital death and 64% and 65% for length of hospitalization >10 days.

Although WRF was clearly associated with poor in-hospital outcomes, it is not clear whether it is a marker of risk or a cause. Nonetheless, it is plausible that interventions that prevent creatinine increases during HF hospitalizations may improve outcomes. Whatever the relationship between creatinine and HF pathophysiology, the possibility that such small increases in creatinine can sensitively predict worse outcomes provides key opportunities to identify patients at risk.

Study limitations. This analysis did not investigate the impact of in-hospital management choices on the risk of WRF. Choices of medications (as well as their timing and doses), concomitant disease, and procedures are all important considerations in assessing changes in renal performance. We were also limited in this retrospective analysis by information that was available in the chart. To improve the specificity of the information, we made use of various

sources, when possible. For example, diabetes was coded only when patients were receiving medications (parenteral or oral) for this condition.

Conclusions. This large and diverse cohort study demonstrates that WRF occurs frequently in hospitalized HF patients and is associated with adverse outcomes. This association remains strong in younger as well as older patients. Significant predictors of in-hospital renal dysfunction include elevated baseline serum creatinine, a history of HF or diabetes, and elevated systolic BP. Relatively small rises in serum creatinine (>0.3 mg/dl [26.5 μmol/l]) have adverse prognostic significance, irrespective of the patient's baseline renal function or peak serum creatinine. Surprisingly, we found no clear relationship between hypotension or the severity of LV systolic dysfunction and the occurrence of WRF. Additional research is required to better delineate in-hospital factors that may precipitate WRF. Furthermore, it will be important to determine whether WRF is itself the cause of increased morbidity and mortality in these patients and, therefore, a potential target for intervention, or if WRF is simply a marker of patients with more severe pathophysiologic derangements.

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