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Relation of Worsened Renal Function during Hospitalization for Heart Failure to Long-Term Outcomes and Rehospitalization

David E. Lanfear, MD MS[a,b], **Edward L. Peterson, PhD**[c], **Janis Campbell**[b], **Hemant Phatak, Ph.D.**[d], **David Wu, Ph.D**[d], **Karen Wells**[c], **John A. Spertus, MD MPH**[e], and **L. Keoki Williams, MD MPH**[b]

[a] Heart and Vascular Institute, Henry Ford Hospital, Detroit MI, 48202

[b] Center for Health Services Research, Henry Ford Hospital, Detroit MI, 48202

[c] Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit MI, 48202

[d] Global Outcomes Research, Merck & Co., Inc., Whitehouse Station, NJ 08889

[e] Mid America Heart Institute, Kansas City MO

Abstract

Worsened renal function (WRF) during heart failure (HF) hospitalization is associated with in-hospital mortality, but there are limited data regarding its relationship to long-term outcomes after discharge. The influence of WRF resolution is also unknown. This retrospective study analyzed patients who received care from a large health system and had a primary hospital discharge diagnosis of HF between 1/2000 and 6/2008. Renal function was estimated from creatinine levels during hospitalization. The first available value was considered baseline. WRF was defined a creatinine increase of ≥0.3mg/dl on any subsequent hospital day compared to baseline. Persistent WRF was defined as having WRF at discharge. Proportional hazards regression, adjusting for baseline renal function and potential confounding factors, was used to assess time to re-hospitalization or death. Among 2465 patients who survived to discharge, 887 (36%) developed WRF. Median follow up was 2.1 years. In adjusted models, WRF was associated with higher rates of post-discharge death or re-hospitalization (HR 1.12, 95%CI 1.02 – 1.22). Among those with WRF, 528 (60%) had persistent WRF while 359 (40%) recovered. Persistent WRF was significantly associated with higher post-discharge event rates (HR 1.14, 95%CI 1.02 – 1.27), whereas transient WRF showed only a non-significant trend towards risk (HR 1.09 95%CI 0.96-1.24). In conclusion, among patients surviving hospitalization for HF, WRF was associated with increased long-term mortality and re-hospitalization, particularly if renal function did not recover by the time of discharge.

Keywords

heart failure; cardiorenal syndrome; mortality; morbidity

Address for Correspondence:David E. Lanfear, Henry Ford Hospital, 2799 W. Grand Blvd., K14, Detroit MI, 48202. dlanfea1@hfhs.org Phone: (313) 916-6375 Fax: (313) 916-8799.

DISCLOSURES
Hemant Phatak, Ph.D. and David Wu, Ph.D. are Merck employees. All other authors have no relationships to disclose.

INTRODUCTION

A recent reanalysis of a clinical trial cohort demonstrated that WRF persisting at hospital discharge is associated with increased risk of death at one year (HR=1.5).[1] This leaves unanswered whether WRF overall is associated with long term outcomes, and the relative contributions of WRF category (persistent vs. transient) to post-discharge outcomes. To clarify these issues we performed a retrospective analysis of all patients hospitalized for HF at our center over an 8 year period, assessing the relationship of WRF in the hospital with long-term death or re-hospitalization.

METHODS

The study was approved by the Institutional Review Board at Henry Ford Hospital. This work was supported by a grant from Merck Inc. Global Outcomes Research, and Dr. Lanfear's effort is supported by an NIH (NHLBI) Career Development Award (K23HL085124).

Using automated data sources, we identified all patients ≥18 with a primary hospital discharge diagnosis of heart failure (see Appendix A for the International Classification of Diseases, 9th Edition/Revision [ICD-9] codes used) between January 1, 2000 and June 30, 2008. The index hospitalization was the first inpatient admission during the period of observation. Patients also had to be members of a health plan for at least one year prior to the index hospitalization and to have received their care through health system physicians. Patients were followed until they reached an endpoint (death or re-hospitalization) or were censored at the earlier of either disenrollment or final follow up on December 31, 2008.

Data for this study came from the following sources: electronic administrative databases maintained by the health system, vital records from the Michigan Department of Community Health, and the Death Master File (DMF) from the Social Security Administration (SSA). The administrative data captured claims (i.e., coded diagnoses, procedures, and prescription fills) occurring both within and outside the health system. A master patient index (MPI) contained demographic data (i.e., date of birth, sex and race). Laboratory data was available for all tests performed within the health system. The DMF, available through the National Technical Information Service, was supplemented with the Michigan State Division of Vital Records and Health Statistics, both or which were queried with patients' social security number.

We obtained all serum creatinine laboratory measurement from the index hospitalization. The first creatinine value during hospitalization or in the emergency department (if that was the route of admission) was considered the baseline value. On each day of hospitalization, the last creatinine measurement was taken as the value for that day. Consistent with prior studies, WRF was defined as a ≥0.3 milligram per deciliter (mg/dl) increase in creatinine on any subsequent hospital day compared to baseline.[2,3] Persistent WRF was defined as the patient meeting the WRF definition at the last available creatinine value during that hospitalization; this was required to be within 24 hours of discharge. If the patient had met WRF definition on any hospital day but no longer met the definition at discharge, they were considered to have transient WRF (i.e., recovery of renal function by discharge).

The covariates examined included age, race, gender, baseline creatinine, and baseline co-morbidities (i.e., prior atrial fibrillation, diabetes, hypertension, vascular disease, stroke, heart failure, and coronary disease). These covariates were included in all multivariate models to assess the independent association between WRF and the outcome under

evaluation. Except for diabetes and hypertension, baseline comorbidities were defined as having a primary or secondary ICD-9 diagnosis in any setting and in the year prior to the index date (i.e., the baseline year). Diabetes mellitus and hypertension required two claims with the relevant ICD-9 diagnostic codes from any clinical setting or at least one primary diagnosis from a hospitalization in the baseline year. Alternatively, a baseline history of diabetes mellitus could be defined as one or more prescriptions filled for a diabetic medication in the baseline year (see Appendix B for the list of medications). Procedure codes (Appendix C) were also used to ascertain the presence of some of the comorbidities.

The primary endpoint was the time to death or re-hospitalization for any cause. Hospital re-admissions were identified from claims data, all of which are available for health plan members enrolled in this study. Deaths were identified using data obtained from health system administrative data, vital records from the State of Michigan, and the SSA DMF, as described above.

WRF categories were compared using either chi-squared tests for categorical variables or two-sample Student's t-tests for continuous variables. Those variables which were not distributed normally were compared using a two-sample Mann-Whitney test. Baseline creatinine values were natural log transformed to normalize their distribution. Event rate estimates were generated using Kaplan-Meier curves and these curves were compared using log-rank tests. Proportional hazards regression models were used to assess the relationship of WRF (WRF vs. no WRF) and WRF category (no WRF vs. transient WRF, vs. persistent WRF) with the composite endpoint of mortality or re-hospitalization following discharge, with adjustment for all baseline covariates including renal function at admission (which was log transformed due to skewed distribution). Logistic regression was used to assess the relationship of baseline patient and clinical factors to persistent WRF. All analyses were performed in SAS version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 2,537 patients were initially identified. Of these, 72 died during the index hospitalization. Among this group WRF was strongly associated with in-hospital death (HR 2.8, 95% CI 1.73 – 4.52), and was associated with a near doubling in length of stay (3.8 vs. 7.0 days, $p<0.001$). Excluding the patients who did not survive to discharge left 2,465 meeting full inclusion criteria. The baseline characteristics of these 2,465 patients who made up the study cohort are shown in Table 1. Overall, 887 (36%) patients developed WRF. This occurred at an average of 2.5 (± 3.73) days of hospitalization. Age, diabetes, loop diuretic use, peripheral vascular disease, and the number of creatinine measurements were associated with WRF in bivariate analyses (all $p<0.05$, Table 1).

During a median follow up of 2.1 years 1,238 patients died and 1,966 were re-hospitalized. Patients with WRF were at increased risk of death or re-hospitalization during follow up ($p<0.001$). The results of multivariable models adjusting for demographics, baseline renal function, hemoglobin, medication use, and comorbidities confirmed that WRF was independently associated with the combined outcome of re-hospitalization or death (HR 1.12, 95% CI 1.02 – 1.22, $p=0.015$) (Table 2). When these outcomes were analyzed individually, WRF showed a similar association with mortality (HR 1.14; 95%CI 1.01-1.28) and with re-hospitalization (HR 1.12; 95%CI 1.02-1.23).

Among the patients who developed WRF, 528 (60%) had persistent WRF at hospital discharge, while 359 (40%) recovered their renal function by the time of discharge (i.e., transient WRF). The bivariate correlates of persistent WRF (vs. transient) are indicated in Table 1. To determine the independent predictors of persistent WRF we used logistic

regression to model persistent WRF (vs. transient WRF) among all WRF patients. African American race (OR 1.71; 95%CI 1.27 – 2.30), older age (OR 1.18 per 10 years in age; 95% CI 1.05 -1.33), and baseline hemoglobin (OR 0.92 per 10 years in age; 95% CI 0.85 - 0.99) were the only factors independently associated with a greater likelihood of persistent WRF.

Survival by WRF category (none, transient WRF, persistent WRF) is shown in Figure 1 (p=0.025). After adjustment for potential confounders (age, sex, race-ethnicity, baseline renal function, hemoglobin, medications, and co-morbidities), persistent WRF was independently associated with an increased risk for the combined outcome of death or re-hospitalization (HR 1.14; 95%CI 1.02-1.27) (Table 3). In contrast, transient WRF did not show a statistically significant association with the rate of these adverse events (HR 1.09; 95%CI 0.96-1.24). To examine whether WRF category (persistent vs. transient) was attributable to differences in initial severity as opposed to recovery, we examined the relationship of baseline, peak, and discharge creatinine in each group. Patients with persistent WRF did have slightly larger magnitude of creatinine change compared to transient WRF (peak-baseline Cr of 0.63 vs. 0.54 mg/dL, p<0.001). However, this difference was modest in comparison to the difference in improvement after peaking, which was much greater in the transient group (peak-discharge Cr of 0.18 vs. 0.57 mg/dl, respectively, p<0.001).

DISCUSSION

This study demonstrates that WRF is an independent predictor of worse long-term outcomes after hospital discharge for HF. The incremental risk could be considered moderate, given the 12% increased hazard of death or hospitalization. Moreover, these data suggest that WRF, as defined in prior studies, is a heterogeneous condition in that the long-term risk is associated with persistent WRF at the time of discharge, but less so with WRF that resolves by the time of discharge.

Our work supplements existing data by establishing the association of WRF to long-term outcomes and exploring the effect of WRF duration. There are two small previous studies suggesting an association of WRF with 1 year outcomes,[4,5] however these were small (the larger had 318 patients) and used an atypical definition of WRF (≥0.3 mg/dL creatinine rise and 25% increase together), one study specifically noting no association when using the 0.3 mg/dL of creatinine definition. Moreover, an examination of the ESCAPE trial showed only a trend towards risk with WRF (defined as ≥0.3 mg/dL rise creatinine) of long term outcomes.[6] Our larger dataset is able clarify this issue, confirming the association of WRF with post-discharge outcomes.

While a persistent decrement in renal function is clearly associated with worse post-discharge outcomes, the relationship of transient WRF to long-term outcomes remains uncertain showing a non-significant trend towards risk in our dataset. Thus, the underlying determinants of WRF duration and how they may relate to outcomes remains an important question. It is possible that persistent vs. transient WRF may be of similar etiology but simply reflect differences in severity of the insult. The maximum change in creatinine was statistically different between persistent vs. transient cases (0.54 vs. 0.63), though whether this is a clinically significant difference is debatable. Many factors underlying WRF in HF have been described including comorbid diseases, the HF disease process itself, hemodynamics, as well as effects of medications.[6–8] Derangements in hemodynamics and neurohormones during acute HF leading to WRF have been termed by some as “vasomotor” nephropathy, which may include interactions with diuretics or other therapy,9 and include several factors that are theoretically reversible. It is tempting to speculate that the transient WRF group may be enriched for patients whose renal injury is related to some of these

reversible insults and that these could be correctible through hydration or by withholding offending medicines. On the other hand, persistent decrements in renal function could possibly be due to insults related to existing comorbidities and aspects of the HF disease process itself that may not be readily reversible.

Regardless of the underlying cause, our data does suggest that those with persistent decrements in renal function during hospitalization are at elevated risk. These patients could be candidates for new interventions or more intense follow up to improve their long-term outcomes, which future studies should focus on. In terms of identifying patients at risk for persistent WRF, we found that African American race, older age, and lower hemoglobin were independent risk factors, with race having the strongest association. While a previous study indicated that baseline renal dysfunction at the time of HF hospitalization was a less important prognostic factor among blacks compared to whites,[10] a test for interaction of race with WRF in our data did not reveal a significant interaction suggesting a consistent impact of WRF across race. Additional investigation is needed to understand why African American patients are at higher risk of persistent decrement in renal function during acute HF, and to reassess whether this translates into disparities in post-hospitalization HF outcomes.

This study has several important limitations that should be considered when interpreting our findings. First, is that it was based on electronic data sources. While this enables large numbers of patients to be studied, the diagnostic misclassification and the lack of robust clinical details of disease severity can limit the fidelity of our analyses. Importantly, in the case for HF, a primary discharge diagnosis (our inclusion criteria) has been shown to have approximately 95% specificity for patients meeting the Framingham definition of HF,11 and in sampling from our own population this criteria was 100% specific.12 Moreover, the diagnostic and procedure codes that we used have been previously demonstrated to be valid. 13 Another concern is that we did not limit rehospitalizations to those for HF only. While this may also be of interest, the authors felt all-cause hospitalization was the preferred endpoint since these patients are at risk for hospitalization due to other conditions, such as renal failure or hypertension, which are equally important to patients and society. Accordingly, the Centers for Medicare and Medicaid Services has chosen all-cause re-hospitalizations as a new outcomes-based measure of healthcare quality in HF. We do not have ejection fraction data so that we cannot perform adjustment of subgroup analysis based on this factor. Finally, all data come from a single center, which raises the question of external generalizability. However these data conform to previous reports in terms of the overall rate of WRF (36%) and its association with increased in-hospital mortality.14

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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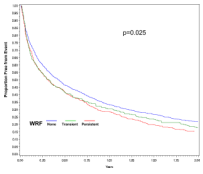

Figure 1.
Freedom from death or re-hospitalization for no WRF vs. transient WRF vs. persistent WRF (n=2465)

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Table 1

Baseline Characteristics by Worsened Renal Function (WRF) Category

Variable	All Patients (n= 2465)	WRF (n=887)	No WRF (n=1578)	Persistent WRF (n=528)	Transient WRF (n=359)
Age, mean ± sd (years)	70.4 + 13.4	**71.2 ± 12.9**	**69.9 ± 13.6**	**72.2 ± 12.5**	**69.8 ± 13.4**
Female	1206 (48.9%)	441 (49.7%)	765 (48.5%)	273 (51.7%)	168 (46.8%)
Race					
Caucasian	1145 (47.7%)	417 (48.7%)	728 (47.2%)	**224 (44.0%)**	**193 (55.5%)**
African American	1256 (51.0%)	440 (49.6%)	816 (51.7%)	**285 (54.0%)**	**155 (43.2%)**
Other	64 (2.5%)	30 (3.4%)	34 (2.2%)	**19 (3.6%)**	**11 (3.1%)**
Baseline creatinine (mg/dl)	1.31 ± 0.59	1.34 ± 0.63	1.29 ± 0.57	1.36 ± 0.69	1.31 ± 0.52
Baseline hemoglobin (g/dl)	12.0 ± 2.0	11.9 ± 2.0	12.0 ± 2.0	**11.7 ± 2.0**	**12.2 ± 2.0**
ACE-I/ARB use during hospitalization	1920 (77.9%)	710 (80.1%)	1210 (76.7%)	415 (78.6%)	295 (82.2%)
Loop diuretic use during hospitalization	2336 (94.8%)	**870 (98.1%)**	**1466 (92.9%)**	518 (98.1%)	352 (98.1%)
Beta blocker use during hospitalization	1224 (49.5%)	428 (48.3%)	796 (50.4%)	251 (47.5%)	177 (49.3%)
Prior Atrial fibrillation	722 (29.3%)	266 (30.0%)	456 (28.9%)	152 (28.8%)	114 (31.8%)
Prior Diabetes	1058 (42.9%)	**406 (45.8%)**	**652 (41.3%)**	244 (46.2%)	162 (45.1%)
Prior Hypertension	1648 (66.9%)	612 (69.0%)	1036(65.7%)	**378 (71.6%)**	**234 (65.2%)**
Prior Peripheral vascular disease	334 (13.6%)	**139 (15.7%)**	**195 (12.4%)**	78 (14.8%)	61 (17.0%)
Prior Stroke	390 (15.8%)	156 (17.6%)	234 (14.8%)	89 (16.9%)	67 (18.7%)

Variable	All Patients (n= 2465)	WRF (n=887)	No WRF (n=1578)	Persistent WRF (n=528)	Transient WRF (n=359)
Prior Heart failure	1229 (49.9%)	439 (49.5%)	790 (50.1%)	252 (47.7%)	187 (52.1%)
Prior Coronary Artery Disease*	749 (30.3%)	284 (32.0%)	464 (29.4%)	172 (32.6%)	112 (31.2%)
Median days in hospital (Q1-Q3)	4 (2-6)	**5 (4-8)**	**3 (2-5)**	**4 (3-7)**	**6 (5-9)**
Proportion of days with Creatinine values	0.927 ± 0.12	**0.914 ± 0.12**	**0.934 ± 0.12**	0.920 ±0.12	0.905 ± 0.11
Median first day w/ WRF (Q1-Q3)	NA	4 (3-6)	NA	**4 (3-7)**	**4 (3-6)**

Worsened Renal Function = any ↑Creatinine ≥ 0.3mg/dL

Bold = p<0.05 (comparison of WRF vs. No WRF; Persistent vs. Transient)

* Prior Coronary Artery Disease defined by ICD-9 or CPT codes for myocardial infarction or coronary revascularization

Table 2

Proportional hazards model of death or re-hospitalization with worsened renal function (WRF) vs. no WRF.

Variable	HR (95% CI)	p-value
Worsened Renal Function	1.12 (1.02 – 1.22)	**0.015**
Baseline Cr (ln transformed*)	1.27 (1.13 – 1.43)	**0.001**
Age (per decade)	1.08 (1.04 – 1.12)	**0.001**
Baseline Hemoglobin	0.95 (0.93 – 0.98)	**0.001**
Stroke	1.25 (1.11 – 1.41)	**0.001**
Heart failure	1.34 (1.21 – 1.47)	**0.001**
Beta Blocker use during hospitalization	0.72 (0.66 – 0.78)	**0.001**
Prior Peripheral Vascular Disease	1.16 (1.02 – 1.37)	**0.025**
Prior Atrial Fibrillation	1.10 (0.99 – 1.22)	0.065
Prior Hypertension	1.08 (0.97 – 1.19)	0.16
Prior Coronary Artery Disease†	1.07 (0.97 – 1.19)	0.183
ACE-I/ARB use during hospitalization	0.94 (0.84 – 1.04)	0.219
Loop diuretic use during hospitalization	1.12 (0.92 – 1.37)	0.26
Diabetes Mellitus	1.05 (0.96 – 1.15)	0.284
African American	0.98 (0.89 – 1.08)	0.656
Female	1.01 (0.92 – 1.11)	0.808

† Prior Coronary Artery Disease defined by any ICD-9 or CPT code for myocardial infarction or coronary revascularization

* The HR reflects a difference in creatinine of 1 vs. 2.72.

Table 3

Proportional hazards model of death or re-hospitalization with persistent worsened renal function (WRF) vs. transient worsened renal function (WRF) (compared to no WRF).

Variable	HR (95% CI)	p-value
Baseline Cr (ln transformed*)	1.27 (1.13 – 1.43)	**0.001**
Persistent WRF	1.14 (1.02 – 1.27)	**0.02**
Transient WRF	1.09 (0.96 1.24)	0.168
Age (per decade)	1.08 (1.04 – 1.12)	**0.001**
Baseline Hemoglobin	0.96 (0.93 – 0.99)	**0.001**
Prior Stroke	1.25 (1.11 – 1.41)	**0.001**
Prior Heart Failure	1.34 (1.21 – 1.48)	**0.001**
Beta Blocker use during hospitalization	0.72 (0.66 – 0.78)	**0.001**
Prior Peripheral Vascular Disease	1.16 (1.02 – 1.32)	**0.024**
Prior Atrial Fibrillation	1.10 (1.00 – 1.22)	0.063
Prior Hypertension	1.08 (0.97 – 1.19)	0.161
Prior Coronary Artery Disease†	1.07 (0.97 – 1.19)	0.187
ACE-I/ARB use during hospitalization	0.94 (0.84 – 1.04)	0.218
Loop diuretic use during hospitalization	1.13 (0.92 – 1.38)	0.254
Prior diabetes	1.05 (0.96 – 1.15)	0.282
African American	0.98 (0.89 – 1.07)	0.635
Female	1.01 (0.92 – 1.11)	0.818

* The HR reflects a difference in creatinine of 1 vs. 2.72.

† Prior Coronary Artery Disease defined by ICD-9 or CPT codes for myocardial infarction or coronary revascularization