Outcome in Acute Heart Failure: Prognostic Value of Acute Kidney Injury and Worsening Renal Function

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ABSTRACT

Background: The prognostic value of worsening renal function (WRF) in acute heart failure is debated. Moreover, it is not clear if the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in this context is detrimental.

Method and Results: In a retrospective cohort study of 646 patients hospitalized for acute heart failure, the risk of death or readmission associated with acute kidney injury (AKI) present at admission, WRF during the 1st 7 days, and up-titration of ACEI/ARB were analyzed in a Cox proportional hazards model. AKI, WRF, hemoglobin concentration, ACEI/ARB up-titration, and use of loop diuretics before admission were significantly associated with the primary outcome in univariate analysis. In a multivariate model, the association remained significant for AKI (hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.13−1.47; $P = .0002$), WRF (HR 1.24, 95% CI 1.06−1.45; $P = .0059$), and ACEI/ARB up-titration (HR 0.79, 95% CI 0.64−0.97; $P = .026$). There was no excess mortality in patients with ACEI/ARB up-titration despite WRF.

Conclusions: Both AKI and WRF are strongly associated with poor outcome in patients hospitalized for acute heart failure. ACEI/ARB up-titration seems to be protective. (*J Cardiac Fail 2015;21:382−390*)

Key Words: Worsening renal function, acute heart failure, prognosis, ACEI/ARB up-titration, readmission, death.

In heart failure patients, chronic renal failure is a well known negative prognostic factor, increasing the risk of all-cause and cardiovascular mortality and hospitalization for worsening heart failure.[1,2] The implications of worsening renal function (WRF) during acute heart failure syndrome is less well characterized.[3] Although many studies and 2 meta-analyses have shown that WRF is associated with in-hospital and post-discharge risk of mortality and readmission in heart failure patients, the exact prognostic implication is still debated.[4,5] In particular, the interaction between WRF and heart failure treatment up-titration is unclear. This latter point has been discussed in the recent literature, but studies on this topic are difficult to generalize, because they are post hoc analyses of randomized clinical trials.[6] We aimed to assess the prognostic value of WRF in a real life cohort of patients hospitalized for acute heart failure syndrome. A secondary aim was to explore the role of up-titration of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on prognosis. Because WRF is frequently observed in patients who have ACEI/ARB up-titration, we tested if the former conveyed the same negative prognostic implication in this subgroup.

Materials and Methods

Design, Population, and Sample Size

We performed a secondary analysis of a cohort of patients admitted for acute heart failure. The initial cohort has been described previously.[7] Briefly, we included consecutive patients presenting to the emergency department of Geneva University

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Hospitals with a chief complaint of dyspnea and a principal diagnosis of heart failure and who were hospitalized. Patients with N-terminal pro−B-type natriuretic peptide (NT-proBNP) plasma levels <300 ng/L before treatment or patients transferred directly to the intensive care unit, including patients with cardiogenic shock or acute coronary syndrome, were excluded. All patients could be included only once.

Follow-Up

Patients were followed for 365 days after admission. Information on death was obtained by consulting the civil status registry office of the State of Geneva. Readmissions were tracked with the use of the electronic database of Geneva University Hospitals, which is the main institution admitting patients for acute heart failure in our region. Follow-up was complete for 586 of the 646 included patients and incomplete for 34. Twenty-six patients were lost to follow-up after hospital discharge. Patients lost at follow-up were right censored.

Variables Definition

An acute decrease of kidney function was defined as either acute kidney injury (AKI) if present at admission or as WRF if it appeared within 7 days after admission. Severity was graded according to the Acute Kidney Injury Network (AKIN) classification.[8] In this classification, an absolute increase in the creatinine value of 26.4 μmol/L, or a relative increase of 1.5−2-fold compared with the baseline creatinine value defines AKIN stage I. A 2−3-fold relative increase defines AKIN stage II and a >3-fold increase or use of dialysis determines AKIN stage III.

We defined AKI as an increase of the creatinine level already present at admission. To determine patient's baseline plasma creatinine level we used the lowest value during the year preceding hospitalization (in 577/646 patients, 89.3%) or, if the former was not available, the lowest creatinine value during the hospital stay (in 69/646 patients, 10.7%). Thus, a patient with AKI had either a creatinine value on admission that was higher than during the preceding year or a high creatinine value on admission that improved or normalized during the hospital stay.

The occurrence of WRF was determined by the difference between the baseline creatinine value (the 1st plasma creatinine available after admission, which was obtained in the emergency room for >90% of patients) and the highest value during the 1st 7 days of hospitalization. WRF could occur in a patient with a normal or elevated creatinine on admission.

The patients could be classified in both AKI and WRF groups if both events occurred (Fig. 1).

Baseline renal function of each patient was described according to the 5 Chronic Kidney Disease (CKD) stages (for details, see Supplemental Table 1). The estimated glomerular filtration rate (eGFR) of each patient was computed by means of the Modification of Diet in Renal Disease (MDRD) formula:

$$\text{eGFR (MDRD)} = 180 \times \text{pCr}^{-1.154} \times \text{age}^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}$$

in which pCr is the plasma creatinine value.[9]

Up-titration of ACEI/ARB was defined in a binary variable by comparing the doses of ACEI/ARB at admission and at discharge for each patient (Supplemental Table 2).

Outcomes

The primary composite end point was the hazard of death or readmission (whichever occurred first) from the 1st day of hospitalization until 365 days. Secondary end point was the hazard of death from the 1st day of hospitalization until 365 days.

Statistical Analyses

Standard descriptive statistics with proportions, medians, and interquartile range were used for baseline characteristics of patients with and without AKI or WRF. We then performed a survival analysis for the main outcome. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed with the use of Cox proportional hazards model to test the univariate association between each variable and the main outcome. The Cox proportional hazard assumption was tested using Schoenfeld (function cox.zph, R package). We repeated the analysis for the hazard of death. We plotted survival curves with the use of Kaplan-Meier estimates, stratifying for the presence of AKI and WRF.

For multivariate analysis, we included variables associated with survival in univariate analysis with a nominal P value of <.05. Variables usually associated with the prognosis in the literature were forced in the model. NT-proBNP was discarded from multivariate analysis owing to missing data and collinearity with other variables. To address the issue of multiple univariate comparisons, the analyses were repeated with the use of only variables significantly associated with the outcome after Bonferroni correction. Models with and without Bonferroni correction did not differ significantly, so only the former are presented.

To address possible collinearity between variables (eGFR, age, and sex), we did a multivariate analysis withholding age and sex, but this did not modify the results, and these variables were therefore kept in the final model. In order to adress possible colinearity between basline renal function assessed by CKD stages and AKI/WRF we did another analysis replacing CKD stages by creatinine value as a continuous variable. The two models produced similar results.

Because intravenous contrast media can be detrimental to renal function, we did a sensitivity analysis by forcing into the model the performance of coronary angiography as a binary variable and by using an interaction term between coronary angiography and WRF.

Finally, we tested whether the up-titration of ARB or ACEI was associated with survival in both groups with and without WRF using Cox proportional hazards assumption.

All analyses were performed with the use of R software (version 2.15.2; http://cran.r-project.org).

This investigation conforms to the principles outlined in Helsinki Declaration. The Ethics Committee for Human Research of the Geneva University Hospital approved the protocol. The need for informed consent was waived.

Results

Patients

Six hundred forty-six patients were included (Table 1). Median age was 80 years, 30.7% of the patients had diabetes, 37.3% had a basal eGFR <60 mL/min, 47.5% had atrial fibrillation, and 43.3% had coronary disease. Chronic obstructive pulmonary disease was present in 16.3% of patients. Regarding cardiac function, 43.2% of patients had preserved left ventricular ejection fraction. Before hospitalization, 40.6% of patients were taking beta-blockers,