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Authors

Griffin, Matthew
Rao, Veena S
Fleming, James
et al.

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Effect on Survival of Concurrent Hemoconcentration and Increase in Creatinine During Treatment of Acute Decompensated Heart Failure

Matthew Griffin, MD[a], **Veena S. Rao, PhD**[a], **James Fleming, BA**[a], **Parinita Raghavendra, MA**[a], **Jeffrey Turner, MD**[b], **Devin Mahoney, BS**[a], **Nicholas Wettersten, MD**[c], **Alan Maisel, MD**[c], **Juan B Ivey-Miranda, MD**[d], **Lesley Inker, MD**[e], **W.H. Wilson Tang, MD**[f], **F. Perry Wilson, MD, MSCE**[b], **Jeffrey M. Testani, MD, MTR**[a]

[a]Sections of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT;

[b]Nephrology, Yale University School of Medicine, New Haven, CT;

[c]Department of Cardiovascular Medicine, Veteran Affairs Medical Center, San Diego, California, USA;

[d]Hospital de Cardiologia, Instituto Mexicano del Seguro Social, Mexico City, Mexico;

[e]Tufts University Medical Center;

[f]Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio

Abstract

Hemoconcentration during the treatment of acute decompensated heart failure (ADHF) is a surrogate for plasma volume reduction and is associated with improved survival, but most definitions only allow for hemoconcentration to be determined retrospectively. An increase in serum creatinine can also be a marker of aggressive decongestion, but in isolation is not specific. Our objective was to determine if combined hemoconcentration and worsening creatinine could better identify patients that were aggressively treated and, as such, may have improved post-discharge outcomes. A total of 4181 patients hospitalized with ADHF were evaluated. Those who experienced both hemoconcentration and worsening creatinine at any point had a profile consistent with aggressive in-hospital treatment and longer length of stay ($p<0.01$), higher loop diuretic doses ($p<0.001$), greater weight ($p=0.001$) and net fluid loss ($p<0.001$) compared to the remainder of the cohort. In isolation, neither worsening creatinine ($p=0.11$) nor hemoconcentration ($p=0.36$) at any time were associated with improved survival. However, patients who experienced both (21%) had significantly better survival (HR=0.80, 95% CI 0.69–0.94, $p_{interaction}=0.005$). In conclusion, this combination of hemoconcentration and worsening creatinine, which can be determined

Address for Correspondence: Jeffrey M. Testani, MD, MTR, Section of Cardiovascular Medicine, Yale School of Medicine, 135 College Street, Suite 230, New Haven, CT 06510, Tel: (215) 459-3709; Fax: (203) 785-4242, jeffrey.testani@yale.edu.

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prospectively during patient care, was associated with in-hospital parameters consistent with aggressive diuresis and improved post-discharge survival.

Keywords

Cardiorenal Syndrome; Venous Decongestion

Introduction

Decongestion is the primary therapeutic goal in the majority of patients with acute decompensated heart failure (ADHF)[1–3], and recent studies have used hemoconcentration as a surrogate for a decrease in plasma volume[4–8]. However, factors unrelated to diuresis such as posture[9], the method and frequency of blood draws[10,11], in addition to the intrinsic variability of the laboratory tests, result in a low signal-to-noise ratio. Furthermore, hemoconcentration in the majority of prior studies was determined from admission to discharge. Using such a definition to prospectively guide de-escalation of diuretic therapy is untenable, since the date of discharge is usually determined at the completion of therapy. Worsening of serum creatinine is common during aggressive diuresis[12], and several studies have reported that the decline in kidney function associated with ADHF treatment is not associated with adverse outcomes[13,14]. However, there are many causes of increased serum creatinine unrelated to decongestion, and so it cannot be recommended in isolation to guide therapy, either. Since different sources of “noise” bias each marker, by combining worsening creatinine with hemoconcentration the signal-to-noise ratio of true decongestion may be improved.

Methods

We reviewed the records of all patients with a primary discharge diagnosis of ADHF who were admitted to the two primary hospitals within the Yale New Haven Health System from February 2013 to September 2015. Inclusion required age of 18 years or older and receipt of intravenous loop diuretics. All patients had at least two hemoglobin, hematocrit, and creatinine values tested in-hospital, one of which was at the time of admission. Patients with a length of stay less than 3 days (who likely underwent limited decongestion) or greater than 14 days (who likely had extreme congestion, or problems unrelated to diuresis) were excluded as per our previous studies on hemoconcentration[15]. Since hemoconcentration assumes stability of absolute red blood cell mass, patients who received a blood transfusion were also excluded. Patients who underwent any type of renal replacement therapy or died during the index hospitalization were excluded (Supplementary Figure 1). In the event of multiple hospitalizations, only the first admission meeting criteria was included. All-cause mortality was determined using the National Death Index.

Hemoconcentration was defined as an increase in both hematocrit and hemoglobin relative to admission levels at any point during the hospitalization. This definition is incrementally different from prior studies, as it can be identified in real-time and not only in a retrospective manner (i.e., admission to discharge). Worsening creatinine was defined as any increase in creatinine above the admission value. Any increase was chosen to maximize sensitivity, as

the physiologic effect we are looking to capture is transient hypovolemia, regardless of whether it progresses to a larger degree of renal dysfunction. Loop diuretic doses were converted to furosemide equivalents using previously published conversions, where 20 mg of torsemide or 1 mg of bumetanide was considered to be equivalent to 40 mg of IV furosemide or 80 mg of oral furosemide[16]. This study was approved by the Yale University Institutional Review Board.

Characteristics are presented as mean ± standard deviation or standard error of the mean, median (interquartile range) or percent. The student's *t* test was used to compare means of independent continuous variables, and the chi-square test was used to evaluate associations between categorical variables. Cox proportional-hazards modeling was used to evaluate associations with all-cause mortality. Candidate covariates entered in the model were baseline characteristics with a theoretical basis for potential confounding, including diabetes, hypertension, obesity (BMI > 30); admission hemoglobin, hematocrit, sodium, estimated glomerular filtration rate, and creatinine; age, race, sex, and length of stay. Adjusted survival curves were plotted for patients with hemoconcentration and worsening creatinine, compared to all others in the cohort. Statistical analysis was performed with IBM SPSS Statistics version 24 (IBM Corporation, Armonk, NY), and statistical significance was defined as 2-tailed $p < 0.05$ for all analyses with the exclusion of tests of interaction where $p < 0.1$ was considered significant.

Results

After application of our exclusion criteria, 4181 patients were analyzed (Supplementary Figure 1). In the cohort, 1507 (36%) of patients achieved hemoconcentration, defined as an increase in both hemoglobin and hematocrit from admission to any point in the hospitalization. 52% had no increase, and 12% had an increase in only one of the two markers. There was a slightly greater incidence in the increase in hematocrit (44%) than hemoglobin (41%). Average relative increases for those who experienced hemoconcentration measured from admission to peak was 8±7% for hematocrit and 7±6% for hemoglobin. 2153 patients (52%) experienced worsening creatinine, defined as any increase in creatinine during the hospitalization. In total 32% of patients (n = 1328) developed worsening creatinine but no hemoconcentration, and 15% (n = 640) experienced hemoconcentration without any change in creatinine, meaning that in total 47% (n = 1968) experienced only one phenomenon. For those who experienced a worsening in creatinine, the median increase was 0.20 mg/dL. In line with the concept that these parameters are providing significantly different information, the correlation between change in hemoglobin ($r=0.06$, $p=0.001$) and hematocrit ($r= 0.09$, $p<0.001$) from day 1 to day 2 was significant but of an extremely modest magnitude, meaning that less than 1% of the variance in hemoglobin or hematocrit is explained by the variance in creatinine.

A total of 867 patients (21%) experienced both hemoconcentration and worsening creatinine. They were on average younger and had a higher baseline eGFR (Table 1). However, despite this they had a significantly lower eGFR on discharge (Figure 1A). These patients also had a greater degree of baseline anemia (Table 1) and, most notably, a longer length of stay (Figure 1B). There were also significant differences in loop diuretic

administration, as those who experienced both hemoconcentration and worsening creatinine received a median daily cumulative dose of 130 mg (IQR 80 mg to 240 mg) furosemide equivalents, compared with 100 mg (IQR 40 mg to 170 mg) in the reminder of the cohort ($p< 0.001$, Figure 1C). This association persisted when controlling for length of stay ($p< 0.001$). Furthermore, patients with both hemoconcentration and worsening creatinine had greater weight loss (2.9 kg± 0.21kg vs 2.0kg ± 0.1kg, $p = 0.041$) and net fluid loss (3399mL ± 176 mL vs 2215mL ± 64mL, $p <0.001$) (Figure 2).

Over a median follow up time of 499 days (IQR 268 days to 786 days), 1103 (26%) patients died from any cause. There was no significant difference in survival between patients with isolated hemoconcentration at any time and all others (HR = 0.94; 95% CI 0.83–1.07, $p = 0.36$). Similarly, there was no difference in survival between patients who experienced isolated worsening creatinine and those who did not (HR = 0.91; 95% CI 0.81–1.02, $p = 0.11$). However, there was a significant interaction between hemoconcentration and worsening creatinine such that patients who experienced both had improved survival compared to those who experienced either hemoconcentration or worsening creatinine, or neither, (HR = 0.80, 95% CI 0.69–0.94, $p_{interaction} = 0.005$, Figure 3). This effect persisted when controlling for baseline characteristics of diabetes, hypertension, obesity (BMI > 30); admission hemoglobin, hematocrit, sodium, estimated glomerular filtration rate, and creatinine; age, race, sex, and length of stay ($p_{interaction} =0.003$, Supplementary Table 1). Furthermore, the interaction remained significant when including only those patients with hospital stays between 3 and 7 days ($p_{interaction} = 0.02$).

Discussion:

The primary finding of this analysis is that patients admitted for ADHF who experience combined hemoconcentration and worsening creatinine at any point during hospitalization had improved survival when compared to all others. Supporting the hypotheses that worsening of creatinine and hemoconcentration are markers of aggressive decongestion and that aggressive diuresis is beneficial, these patients received higher cumulative loop diuretic doses, had a longer length of stay, in conjunction with greater weight and fluid loss. When taken together, these findings suggest that the survival benefit may not have been driven simply by identification of patients with less severe disease, but that patients with combined hemoconcentration and worsening creatinine were more aggressively treated.

The cause of the rise in creatinine attributed to aggressive diuresis is hypothesized to be different from an increase of similar magnitude associated with other mechanisms of acute kidney injury. Prior studies have similarly demonstrated that the decline in GFR that occurs in the setting of aggressive diuresis does not carry a comparatively worse prognosis, nor is it associated with renal tubular injury biomarkers[17–22]. Furthermore, several studies including a post-hoc analysis of the DOSE trial demonstrated improved eGFR during hospitalization was a predictor of worse outcomes, including higher rates of mortality[13,17,18,23]. A plausible explanation for this last finding is that the improvement in eGFR came at the expense of complete diuresis, leading to residual congestion. Conversely, worsening of creatinine may serve as a marker that the kidneys are sensing an absolute reduction in intravascular or total body volume.

Hemoconcentration is by definition a relative marker of the change in intravascular volume. As such, the change in hemoglobin or hematocrit cannot distinguish euvolemia from improvement in persistent hypervolemia. In the majority of prior hemoconcentration studies, it was assessed from admission to discharge, anchoring the finding of hemoconcentration to the physician's subjective determination that the patient reached an acceptable absolute threshold of euvolemia. Notably, in our prior study where we examined hemoconcentration at any time during the hospital stay, this was not associated with improved outcomes; only hemoconcentration occurring toward the end of hospitalization was associated with a survival benefit. In the current analysis, a rise in creatinine may provide similar incremental information. Within healthy adults, the kidney maintains a very narrow range of absolute intravascular volume, and thus an increase in creatinine may serve as a marker that is not only independent from hemoconcentration, but also allows for some degree of information related to the absolute volume status to be paired with the relative.

These results may represent a step forward in moving hemoconcentration closer to becoming a prospective tool that can be used guide patient care. Combining two readily-available, independent markers that have a plausible mechanism for measuring both relative and absolute changes in intravascular volume mitigates the limitation of each marker in isolation. Importantly, as laboratory measurements, they are subject to less variation than traditional metrics of decongestion such as weight and net fluid balance, which are known to have low fidelity[24,25]. Most importantly and in contrast to prior studies of hemoconcentration, this is a definition that can be applied prospectively. Taken as a whole, this biology and congruent associations in this manuscript suggest prospective study of combined hemoconcentration and worsening creatinine may be warranted to validate these hypothesis-generating findings.

This is a retrospective analysis, which, by definition cannot establish causality. Data was obtained from the electronic medical record thus relying on International Classification of Diseases (ICD) codes to ascertain comorbidities, resulting in the known limitations associated with this approach. Physicians were not blinded to the results of either serum marker and may have modified treatment in response to these changes. There were no direct measurements of volume performed, so it cannot be determined definitively from this analysis that combined hemoconcentration and worsening creatinine actually resulted in improved intravascular volume. Lastly, it remains to be seen whether using our proposed metric prospectively to guide treatment would provide the same mortality benefit. As a result of these limitations, these findings are hypothesis-generating only and would need further prospective validation prior to clinical application.

In conclusion, the combination of hemoconcentration and worsening creatinine is associated with improved post-discharge survival in an ADHF cohort. Furthermore, this subset of patients received higher doses of diuretics, had a longer length of stay and experienced greater fluid and weight loss, suggesting the hypothesis that this benefit may have been mitigated by intensity of therapy. Additional research is necessary to understand the utility of this approach in guiding ADHF therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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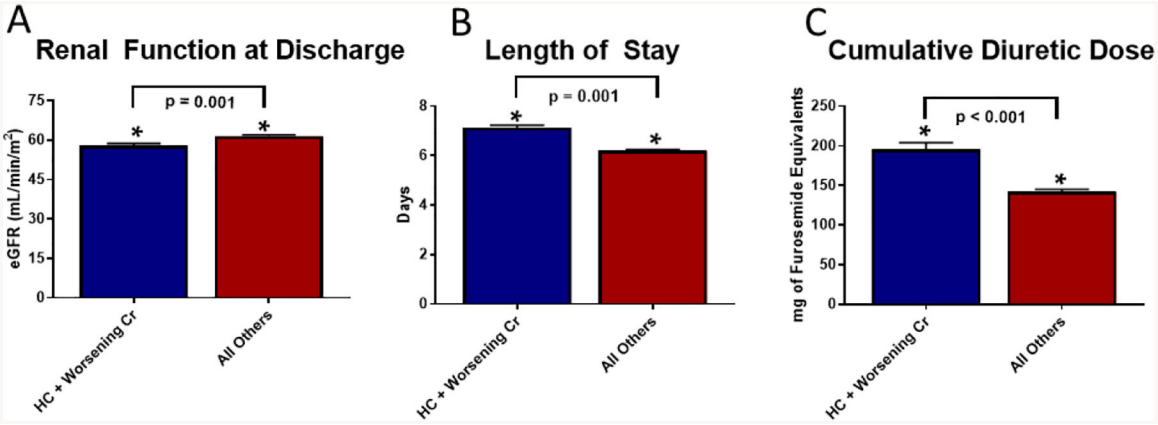

Figure 1. Differences at Discharge Between Patients with Both Hemoconcentration and Worsening Creatininevs. All Others:

1A. Patients who achieved hemoconcentration and experienced worsening creatinine had lower eGFRs at discharge (62mL/min/1.73m^2 vs 58mL/min/1.73m^2, p= 0.001), despite having higher eGFRs on admission; **1B**. They also had longer lengths of stay (7.1 days vs 6.2 days, p= 0.001); **1C**. They received higher cumulativediuretic doses in furosemide equivalents (196 mg vs 142 mg, p < 0.001), 1C.

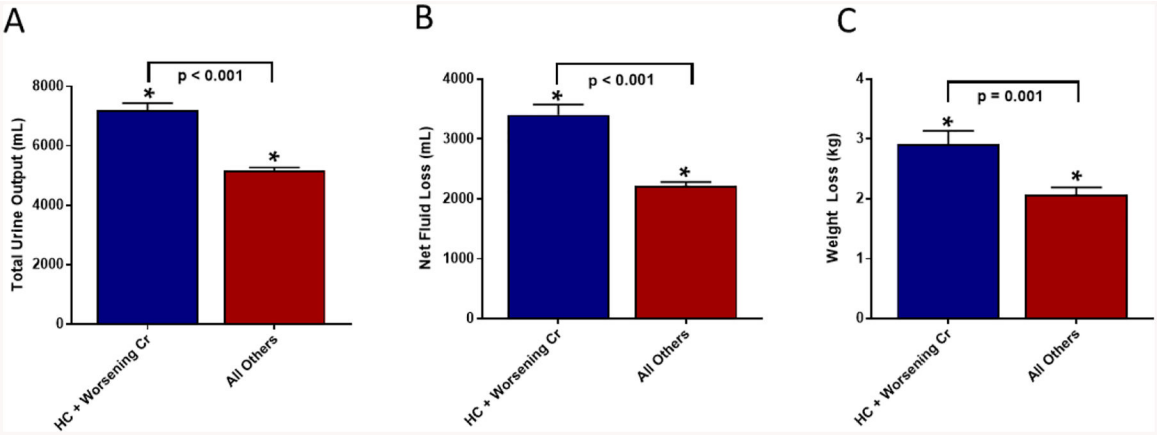

Figure 2. Comparisonof Fluid-Loss Metrics between Patients with Both Hemoconcentration and Worsening Creatinine (Cr) vs. All Others:

Patients who achieved hemoconcentration and experienced worsering creatinine produced more urine than all others (7188 mL vs 5176mL, p< 0.001; **A**. The also had greater net fluid loss (3399mL ± 176 mL vs 2215mL ± 64mL, p <0.001; **B** and weight loss (2.9 kg± 0.21kg vs 2.0kg ± 0.1kg, p = 0.001; **C**. These effects persisted when controlling for length of stay (p<O.OOl for fluid loss and urine output, p = 0.041 for weight loss)

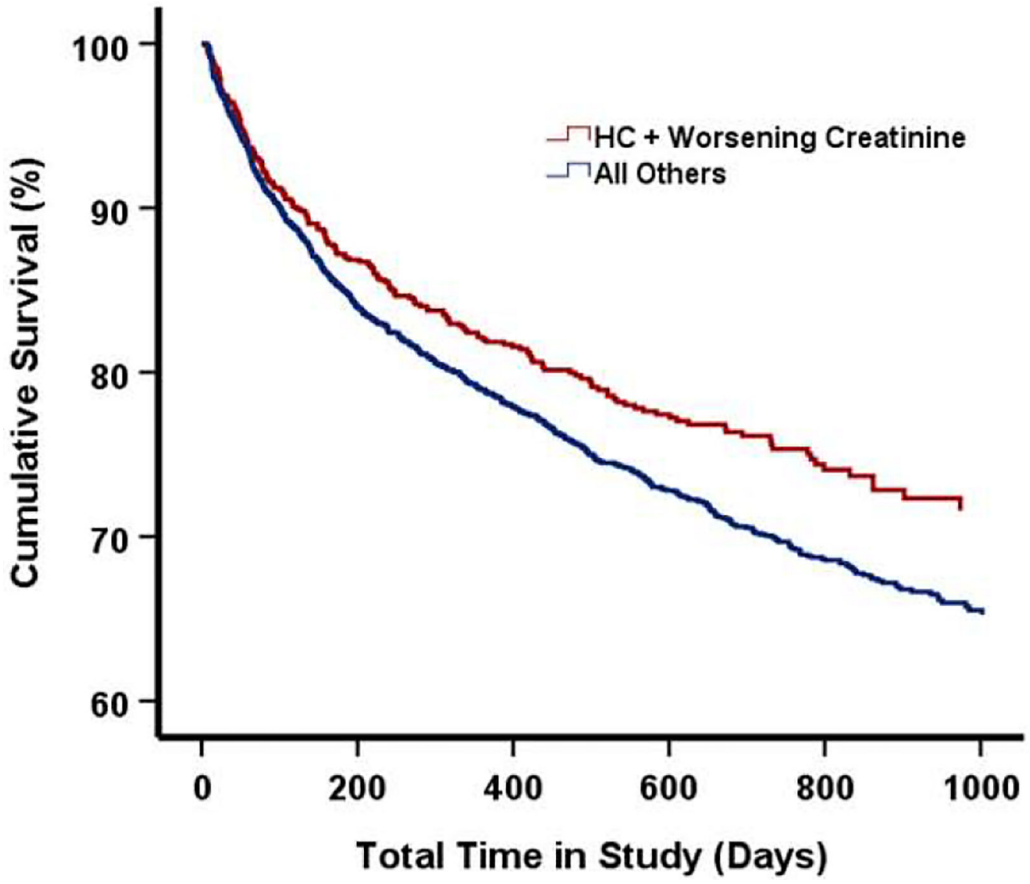

Figure 3. Cumulative Survival of Patients with Hemoconcentration and Worsening creatinine Compared with All Others.

Those who experienced both hemoconcentration and worsening creatinine experienced a significant survival advantage over those who did not (HR = 0.80, 95% Cl 0.69–0.94, $p_{interaction}$= 0.005). This effect persisted when controlling for baseline characteristics of diabetes, hypertension, obesity; admission hemoglobin, hematocrit, sodium, estimated glomerular filtration rate, and creatinine; age, race, sex, and length of stay **(**$p_{interaction}$ =0.003).

Table 1:

Baseline Characteristics of Study Population According to Hemoconcentration and Worsening Creatinine

Characteristics	Hemoconcentration and worsening creatinine (N= 867)	All Others (N = 3314)	*P*
Age (years)	75 ±15	76±14	<0.01 *
White	85%	86%	0.65
Women	52%	53%	0.49
Obesity †	20%	19%	0.61
Hypertension	49%	47%	0.31
Diabetes Mellitus	39%	39%	0.93
Peripheral Vascular Disease	16%	12%	0.95
Depression	15%	16%	0.60
Elixhauser Comorbidity Index	5.8 ±2.0	5.7 ±1.9	0.19
Systolic Blood Pressure (mmHg)	137 ±27	137 ±27	0.64
Diastolic Blood Pressure (mmHg)	74 ±17	75 ±18	0.99
Heart Rate (beats per minute)	85 ±21	87 ±22	0.02 *
Hemoglobin (g/dL)	11.8 ±1.9	12.3 ±2.0	<0.01 *
Hematocrit (%)	35.7 ±5.6	37.6 ±6.2	<0.01 *
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)	64 ±27	55 ±25	<0.01 *
Sodium (mmol/L)	138 ±5	138 ±5	0.32
Blood Urea Nitro gen (mmol/L)	26 ±15	29.9 ±18	<0.01 *
Albumin (g/dL) *	3.5 ±0.5	3.5 ±0.5	0.63

† Obesity is Defined as Body Mass Index > 30 kg/m2

* Albumin levels available in 2437/4181 patients; eGFR = estimated glomerular filtration rate