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Heart Failure Outcomes With Volume-Guided Management

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ABSTRACT

OBJECTIVES This study performed a retrospective outcome analyses of a large cohort of mixed ejection fraction patients admitted for acute heart failure (HF), whose inpatient care was guided by individual quantitative blood volume analysis (BVA) results.

BACKGROUND Decongestion strategies in patients hospitalized for HF are based on clinical assessment of volume and have not integrated a quantitative intravascular volume metric.

METHODS Propensity score control matching analysis was performed in 245 consecutive HF admissions to a community hospital (September 2007 to April 2014; 78 ± 10 years of age; 50% with HF with reduced ejection fraction [HFrEF]; and 30% with Stage 4 chronic kidney disease). Total blood volume (TBV), red blood cell volume (RBCV), and plasma volume (PV) were measured at admission by using iodine-131-labeled albumin indicator-dilution technique. Decongestion strategy targeted a TBV threshold of 6% to 8% above patient-specific normative values. Anemia was treated based on cause. Hematocrit (Hct) measurements were monitored to assess effectiveness of interventions. Control subjects derived from Centers for Medicare and Medicaid Services data were matched 10:1 for demographics, comorbidity, and year of treatment.

RESULTS Although 66% of subjects had PV expansion, only 37% were hypervolemic (TBV >10% excess). True anemia (RBCV ≥10% deficit) was present in 62% of subjects. Treatment of true anemia without hypervolemia resulted in a rise in peripheral Hct of 2.7 ± 2.9% ($p < 0.001$), and diuretic treatment of hypervolemia in cases without anemia caused a 4.5 ± 3.9% ($p < 0.001$) increase in peripheral Hct at 11.3 ± 7.5 days after admission. Subjects had lower 30-day rates of readmission (12.2% vs. 27.7%, respectively; $p < 0.001$), of 30-day mortality (2.0% vs. 11.1%, respectively; $p < 0.001$), and of 365-day mortality (4.9% vs. 35.5%, respectively; $p < 0.001$) but longer lengths of stay (7.3 vs. 5.6 days, respectively; $p < 0.001$) than control subjects.

CONCLUSIONS Retrospective outcomes using volume-guided HF therapy versus propensity-matched controls support the benefit of BVA in guiding volume management and reducing death and rehospitalization due to HF. (J Am Coll Cardiol HF 2018;6:940–8) © 2018 by the American College of Cardiology Foundation.

Effective management of patients hospitalized for acute heart failure (AHF) remains problematic despite advances in medical therapy. Survival after the first admission remains poor, with 1-year mortality reported at 30% (1). The mainstay of treatment remains diuresis, which has been associated with increased mortality (2). Worsening renal function is also a common complication of treatment and is itself associated with increased morbidity, mortality, and economic burden (3). AHF in the United States represents $21 billion in direct costs and $10 billion in indirect costs annually with up to 80% attributable to direct costs secondary to hospitalization (4).

Heart failure is recognized as a syndrome that is diverse in causes in which multiple comorbidities complicate clinical presentation (5–9). However, the precipitation of acute decompensation is commonly a condition of volume overload. American College of Cardiology/American Heart Association guidelines have long recommended volume status be assessed at every patient encounter (10). This imperative poses challenges in clinical practice, as interpreting the signs and symptoms of congestion is neither sensitive nor

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specific (6,7,11) including surrogates of volume status, such as physical signs, invasively obtained hemodynamic metrics, biomarkers, thoracic impedance, and hemoglobin (Hb) and hematocrit (Hct) measurements. Calculated intravascular volume estimates have been reported in many analyses but have not been shown to be consistently correlated or serve as accurate reflections of intravascular blood volume status (6,9,12–19). Research comparing direct quantitative blood volume analysis with standard-of-care assessment has shown that experienced cardiologists correctly categorize patients as hypervolemic, hypovolemic, or euvolemic only half the time (7). Adequacy of diuresis is also difficult to evaluate, as multiple observational studies show patients are commonly discharged on the basis of clinical assessment, although their volumes are still severely overloaded (7,20–22).

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Miller et al. (8,9,20,23), using quantitative volume analysis, demonstrated that a marked heterogeneity in volume status exists in AHF. Total blood volume (TBV) varies from normal to marked excess with heterogeneity evident not only in plasma volume (PV) but also in a spectrum of intravascular red blood cell volume (RBCV) derangements. The fundamental issue of underlying volume heterogeneity in patients with clinical presentation of fluid overload delineates the core challenge of managing AHF. To date, the limited success of efforts to improve outcomes through "one-size-fits-all" diuretic strategies suggests an unmet clinical need for a more individualized approach (8,9,24).

Accordingly, we undertook retrospective outcomes analysis of a large cohort of patients with mixed ejection fraction (EF) admitted for AHF whose inpatient care was guided by quantitative results of blood volume analysis (BVA). Initially, we compared cohort data with those of Medicare institutional and national benchmarks for 30- and 365-day outcomes (25). Multivariate propensity-matched control analysis was undertaken to confirm earlier findings. Our working hypothesis was that individualized care guided by direct quantitative volume measurement would demonstrate improvements in short- and long-term all-cause mortality, 30-day rehospitalizations, and length of stay (LOS).

METHODS

Admissions to a community hospital HF service over a period of 6.5 years (September 2007 to April 2014) were retrospectively analyzed. The study cohort consisted of 245 consecutive admissions representing 177 unique patients. No study patient was a participant in a previous clinical trial or included in a previous publication. Intravascular volume was measured shortly after admission by using an iodine-131-labeled human serum albumin indicator-dilution technique (Daxor Corporation, New York, New York), and results were used to guide treatment. EF was measured in all patients through echocardiography. Management strategies were determined for each patient based on measured derangements of TBV and RBCV. The degree of hypervolemia (percent of excess in TBV vs. patient-specific normative value) confirmed the need for diuresis, and decongestive treatment was planned to target a TBV slightly above patient-specific normative volume at volume expansion of approximately +6% to +8%. True anemia was identified, quantified, and treated by intravenous administration of iron in iron-deficient patients, with or without epoetin administration, and packed red blood cell transfusion for the most severe cases (Hb <8 g/dl). Polycythemic patients (RBCV deviation from ideal >+10%) were treated by phlebotomy after appropriate decongestion to return RBCV to near normal. Knowledge of the initial RBCV allowed diuretic therapy to be guided to achieve target TBV by comparing follow-up peripheral Hct (pHct) values with normalized Hct (nHct) (defined as the Hct level that would be measured if RBCV remained constant and PV was adjusted so that TBV was normal). Once the initial BVA test was performed, the readily available pHct test results provided an updated view of the patient's volume status, so that, in those cases where it could be assumed that RBCV was reasonably stable (absent bleeding or interventions to correct anemia), an increase in pHct could be interpreted as a true (decongestive) decrease in PV. For patients with BVA-confirmed hypervolemia (TBV >10% excess) and no evidence of bleeding, diuresis was continued until pHct rose to within 4 to 8 percentage points of the nHct. In many patients this change was observed late in the course of diuresis after an initial period of stable pHct. In most cases, initial BVA results provided sufficient guidance for both decongestion and treatment of RBCV disturbances. A follow-up BVA was performed only on the basis of new or worsening symptoms, worsening renal function, weight gain, or concern for potential bleeding (<2% of admissions); 18 patients (7%) underwent subsequent BVA on an outpatient basis (mean: 38.5 days post-discharge) to monitor recovery, assess adequacy of treatment, or further optimize treatment. Hospital readmissions were determined by Centers for Medicare and

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

BVA = blood volume analysis

ICD-9 = International Classification of Diseases-9th Revision

PV = plasma volume

RBCV = red blood cell volume

TBV = total blood volume

TABLE 1 Propensity-Matched Control Comparisons of Population Characteristics

	BVA-Guided Subjects (n = 245)	Control Subjects (n = 2,450)	p Value
Demographics			
Age	77.96	78.17	0.76
Male	0.58	0.56	0.61
White	0.96	0.97	0.31
Black	0.02	0.02	0.49
Hispanic	0.02	0.01	0.46
Treatment year			
2010*	0.53	0.53	0.89
2011	0.15	0.16	0.62
2012	0.20	0.19	0.68
2013	0.09	0.10	0.63
Morbidity index			
Charlson	2.76	2.77	0.93
Quan	2.82	2.85	0.72
van Walraven	14.49	14.73	0.56
Specific comorbidities‡			
CHF	0.94	0.94	0.98
Cardiac non-HF	0.03	0.03	0.95
Cardiac arrhythmias	0.58	0.61	0.35
Valvular disease	0.32	0.32	0.96
Pulmonary circulation disorders	0.12	0.11	0.69
Peripheral vascular disorders	0.11	0.11	0.95
Hypertension, uncomplicated	0.38	0.41	0.35
Hypertension, complicated	0.24	0.24	0.95
Chronic pulmonary disease	0.03	0.03	0.94
Diabetes, uncomplicated	0.24	0.23	0.97
Diabetes, complicated	0.07	0.07	0.76
Hypothyroidism	0.08	0.09	0.93
Renal failure	0.27	0.27	0.76
Fluid and electrolyte disorders	0.26	0.26	0.93

*Available CMS data for 2007 to 2009 were limited to one-quarter of admission rather than exact admission dates, precluding calculation of intervals between admission and outcomes; thus, patients treated 2007 through 2010 were grouped and were considered to have been treated in 2010; of the 130 patients treated in 2010 and previously, 58 were treated in 2009, 32 in 2008, and 1 in 2007. p Values throughout are according to 2-way Student's *t*-test. ‡Incidence of additional comorbidity control factors were used in both subjects and control patients <5%, and with p values >0.50, that is: paralysis, neurological disorders; other, liver disease, peptic ulcer disease, HIV/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression.

BVA = blood volume analysis; CHF = congestive heart failure; HF = heart failure.

Medicaid Services (CMS) methods as endorsed by the National Quality Forum (26).

STATISTICAL ANALYSES

To obtain propensity score-matched controls, application was made to and granted by CMS to use a Limited Data Set, LDSS-2017-50679. Anonymized patient data for 2007 to 2015 covering hospital inpatient care ("Inpatient" and "Denominator" files) were obtained with a 5% extraction and, using CMS-recommended procedures (26,27), processed to identify and quantify readmission and mortality events. Post-processing, the dataset contained 3,564,276 hospital admissions from 2010 to 2015, representing 1,194,095 unique patients. Each record contained all diagnostic codes for the original admission as well as for relevant readmission, if any. Statistical software (R software, Vienna, Austria) was used, supplemented with specialized R software, International Classification of Diseases (ICD) was used to specify diagnostic codes, and MatchIt (R software) was used for selecting propensity-matched controls. During the years covered by the study only ICD-9 (9th Revision) codes were in place, thus these were used exclusively. For both study and control patients, all ICD-9 codes in patient records pertaining to an admission were used to calculate comorbidities. For each admission, a single comorbidity score was calculated according to scores from studies by Charlson et al. (28), Quan et al. (29), and van Walraven et al. (30), and specific comorbidity states by Quan's comorbidity mappings based on Elixhauser (Quan Elix) (29) (**Table 1**) were used to characterize admissions and readmissions as HF-related, cardiac but non-HF-related (coded for arrhythmia or valvular comorbidities, but not congestive heart failure [CHF]), or other (e.g., absence of CHF, arrhythmia, and valvular comorbidities). Propensity matching controlled for demographics (age, sex, race), overall comorbidity score (Charlson, Quan, van Walraven indices), specific comorbidities (Quan Elix), and year of treatment, using "nearest neighbor" methodology with a ratio of 10:1 and a control cohort of 2,450 subjects selected to match the 245 study admissions.

The assumption that the control population selected by the MatchIt process matched the subject population was validated by computing p values using a 2-sided Student's *t*-test for each of the control variables (**Table 1**). The lowest p value observed was 0.31 among 45 control variables. Similar results were obtained for the match performed for the LOS subset ≥3, in which 180 subjects were matched to 1,800 control subjects; the lowest p value observed was 0.39 among 45 control variables.

The assumption that treatment status (volume-guided subjects vs. non-volume-guided controls) determined outcomes was validated by using two methods. The first method computed p values by using a 2-sided Student's *t*-test of each individual outcome. These p values are quoted in the abstract and throughout the text. (In **Table 2**, where outcomes are shown for various clinical factors such as blood volume status and EF, which are known for the subjects but unknown for the control subjects, p values were computed by comparing each subject subset with the entire control group.)

TABLE 2 Outcomes for Volume-Guided Subjects by Patient and Blood Volume Characteristics

			30-Day Readmissions		30-Day Mortality		365-Day Mortality	
	N = 245	% of N	Rate (%)	p Value	Rate (%)	p Value	Rate (%)	p Value
Overall			12.2	<0.001	2.0	<0.001	4.9	<0.001
Sex								
Female	103	42	9.7	<0.001	1.0	<0.001	2.9	<0.001
Male	142	58	14.1	<0.001	2.8	<0.001	6.3	<0.001
Age, yrs								
<75	87	36	8.0	<0.001	1.1	0.001	3.4	<0.001
≥75	158	64	14.6	<0.001	2.5	<0.001	5.7	<0.001
LOS								
0 days	41	17	7.3	0.002	2.4	0.082	2.4	<0.001
1–2 days	24	10	20.8	0.648	0.0	0.103	0.0	<0.001
3+ days	180	73	12.2	<0.001	2.2	<0.001	6.1	<0.001
TBV								
Euvolemic or hypovolemic	154	63	11.7	<0.001	1.9	<0.001	5.2	<0.001
Hypervolemic	91	37	13.2	0.001	2.2	0.004	4.4	<0.001
RCV								
Anemic	151	62	11.9	<0.001	2.6	<0.001	6.6	<0.001
Normal RCV	66	27	13.6	0.009	1.5	0.009	3.0	<0.001
Polycythemic	28	11	10.7	0.055	0.0	0.067	0.0	<0.001
TBV and RCV								
Euvolemic or hypovolemic and anemic	122	50	12.3	<0.001	2.5	0.001	5.7	<0.001
Euvolemic or hypovolemic and normal RCV	29	12	10.3	0.037	0.0	0.069	3.4	<0.001
Euvolemic or hypovolemic and polycythemic	3	1	0.0	0.566	0.0	1.000	0.0	0.557
Hypervolemic and anemic	29	12	10.3	0.037	3.4	0.366	10.3	0.003
Hypervolemic and normal RCV	37	15	16.2	0.142	2.7	0.119	2.7	<0.001
Hypervolemic and polycythemic	25	10	12.0	0.115	0.0	0.105	0.0	<0.001
EF								
rEF (<40)	123	50	14.6	<0.001	3.3	0.004	5.7	<0.001
pEF (≥40)	122	50	9.8	<0.001	0.8	<0.001	4.1	<0.001

The p values for all subgroups were calculated in comparison with outcome rates for the complete control group.
pEF = preserved ejection fraction; rEF = reduced ejection fraction; LOS = length of stay; RCV = red cell volume; TBV = total blood volume.

The second method involved performing multivariate linear analysis for each outcome on the mixed dataset that included subjects and controls, with treatment status used as an explanatory variable alongside control variables. Although many control variables were logical (TRUE/FALSE), logistic regression was not used as certain critical control variables (age and morbidity scores) were continuous; logical variables were coded as (1/0). Calculations were performed using the linear modeling function, lm, of R software. Results are shown in Table 3 and in the text. The p values are 2-sided. For each outcome, treatment status was significant at p value <0.001.

RESULTS

Clinical characteristics and demographic features for the study cohort (N = 245) and propensity-matched controls (N = 2,450) are shown in Table 1. Mean values were well matched for all characteristics, and no statistically significant differences emerged.

Study cohort patients experienced markedly better outcomes than control patients for rates of 30-day readmissions (12.2% vs. 27.7%, respectively; p < 0.001), 30-day mortality (2.0% vs. 11.1%, respectively; p < 0.001), and 365-day mortality (4.9% vs. 35.5%, respectively; p < 0.001) (Figure 1) and an increase in LOS versus that in control patients (7.3 vs. 5.6 days, respectively; p < 0.001) (Figure 1).

Table 3 shows variables with a significant impact on outcomes in multivariate analysis. As expected, age was significant for mortality outcomes and Charlson comorbidity score for 30-day mortality. Male patients had somewhat worse outcomes, but sex was nonsignificant in multivariate analysis.

Volume-guided subjects experienced rates of 30-day noncardiac readmissions (4.5% vs. 3.5%, respectively; p = 0.48) comparable to those of controls subjects. The reduction in 30-day readmissions can be attributed to lower rates of HF readmissions (6.1% vs. 20.2%, respectively; p < 0.001) and of cardiac non-HF readmissions (1.6% vs. 3.9%, respectively; p = 0.012)

TABLE 3 Multivariate Analysis of Factors Contributing to the Observed Outcomes in Volume-Guided Patients

Variables Significant for Each Outcome*	Coefficient	p Value
30-day mortality		
Subject (volume-guided treatment)	−0.9	<0.001
Age	+0.003	<0.001
Charlson comorbidity score	+0.046	<0.001
Hypertension, uncomplicated	−0.04	0.001
Diabetes, uncomplicated	−0.07	<0.001
Diabetes, complicated	−0.11	<0.001
365-day mortality		
Subject (volume-guided treatment)	−0.31	<0.001
Age	+0.009	<0.001
Hypertension, uncomplicated	−0.12	<0.001
Hypertension, complicated	−0.08	0.01
Weight loss	+0.62	0.03
30-day readmission		
Subject (volume-guided treatment)	−0.16	<0.001
Hypertension, uncomplicated	−0.07	<0.001
Hypertension, complicated	−0.07	0.03
Paralysis	+0.70	0.02
Solid tumor without metastasis	+0.34	0.03
Coagulopathy	+0.33	0.03
Weight loss	+0.57	0.05
LOS		
Subject (volume-guided treatment)	+1.7	<0.001
Hypertension, uncomplicated	−1.5	<0.001
Hypertension, complicated	−0.9	<0.001
Diabetes, complicated	+1.2	0.05
Hypothyroid	−0.9	0.03
Weight loss	+14.7	<0.001

*All variables, except for age and Charlson comorbidity score, were set at 0 or 1 (indicating absence or presence of a condition), so coefficients convey relative impact.

versus those of controls, supporting the hypothesis that volume-guided management is more effective than standard-of-care management.

Table 2 shows subset outcomes. The p values show comparisons between treated subsets and overall control population, as TBV, RBCV, and several other values were unknown for control patients. No statistically significant outcome differences between subsets in any category were observed among treated subjects.

Marked volume heterogeneity was evident. Although 66% of admissions had some degree of PV expansion, only 37% were actually hypervolemic (TBV in excess of >10% vs. patient normative value). Sixty-two percent had true anemia (RBCV deficit of >10% vs. patient normative value). The combination of hypervolemia and anemia, as defined by volume measurements, was observed in 12% of patients. Another 10% demonstrated hypervolemia and polycythemia.

LOS analysis revealed that same-day discharge (LOS = 0) was recorded for 16.7% of subjects and 1.4% of matched control subjects ($p < 0.001$). Patients discharged on the same day were generally scheduled for close outpatient follow-up. Subjects with LOS = 0 ($n = 41$) experienced lower 30-day event rates than control subjects, with readmission at 7.3% versus 32.4%, respectively ($p = 0.005$), and mortality at 2.4% versus 29.4%, respectively ($p < 0.001$). Multifactor analysis of LOS for study patients showed that LOS was 2.3 days longer for true anemia patients ($p = 0.031$) and 3.0 days longer for patients with severe excess PV (defined as >24% PV according to BVA report; $p = 0.005$). Coefficients for age, sex, EF, and Charlson morbidity score were not statistically significant.

Health economic considerations may affect characterization of shorter stays (31), and particularly, in patients seen in the emergency department with a HF diagnosis may appear in CMS records as outpatients rather than inpatients and, hence, would not have been part of the potential matching population. Consequently, considering the divergence between subjects and control patients with shorter stays in incidence and LOS distribution, matching was re-run for the subset of admissions, resulting in longer stays only (LOS ≥3; $n = 180$) to confirm findings. Results were consistent with those observed overall: the longer LOS subset compared with longer LOS control patients had higher LOS (9.7 vs. 7.2 days, respectively; $p < 0.001$) and lower rates of 30-day readmission (12.2% vs. 26.8%, respectively; $p < 0.001$), 30-day mortality (2.2% vs. 12.5%, respectively; $p < 0.001$), and 365-day mortality (6.1% vs. 40.8%, respectively; $p < 0.001$).

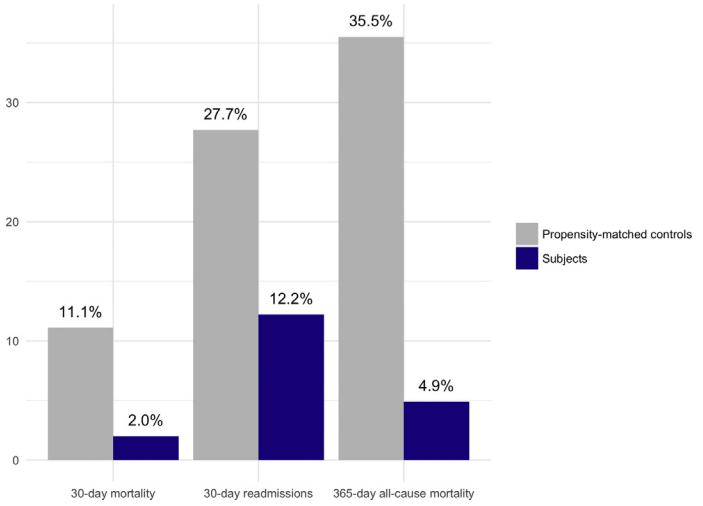
High heterogeneity in volume status was observed across EF subsets, and both HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) had better outcomes than control subjects ($p < 0.001$). HFpEF outcomes were numerically but not statistically superior to those for HFrEF. The 30-day readmissions rates for HFpEF versus those for HFrEF were 9.8% versus 14.6%, respectively ($p = 0.253$), 30-day mortality rate 0.8% versus 3.3%, respectively ($p = 0.179$), and 365-day mortality rates were 4.1% versus 5.7%, respectively ($p = 0.565$).

Follow-up pHct values were measured in all patients, and the maximum Hct achieved during active treatment was recorded (11.3 ± 7.5 days after admission; for 71% of patients, maximum Hct level occurred after hospital discharge), along with the change in pHct from the time of initial blood volume measurement. Table 4 shows these data separated by anemia and hypervolemia status. Patients with neither anemia nor hypervolemia ($n = 32$) had the shortest LOS (5.7 days) and no significant change in Hct. Anemic patients without hypervolemia ($n = 122$) experienced an

increase of 2.7 ± 2.9% ($p < 0.001$) in their pHct levels with early treatment of the anemia. Hypervolemic patients showed a significant increase in pHct with diuretic treatment of their hypervolemia, whether anemia was present (4.4 ± 2.4; n = 29; $p < 0.001$) or absent (4.5 ± 3.9; n = 62; $p < 0.001$). Decongestion of hypervolemic patients without anemia was associated with a partial correction of the PV excess as indicated by the difference between nHct and pHct (which went from 11.1 to 6.6). Decongestion and red blood cell interventions for hypervolemic and anemic patients brought the follow-up Hct level close to that of nHct (the difference went from 5.4 to 0.9). The longer LOS associated with anemia and hypervolemia as seen in multifactor analysis above is also shown in Table 4.

The extent to which knowledge of TBV status guided the diuretic treatment for AHF subjects was confirmed in all patient records by determining whether diuresis was stopped or reduced from its pre-BVA level (low diuretics) or maintained or increased from its pre-BVA level (high diuretics). Of 154 euvolemic or hypovolemic patients (TBV deviation <10%), 124 patients (81%) had their diuretic dosage lowered or diuresis stopped after the initial blood volume analysis. All 91 hypervolemic patients (TBV deviation ≥10%) had their diuretic dosage maintained or increased after the initial BVA.

FIGURE 1 Comparison Between Outcomes of Volume-Guided Patients and Propensity-Matched Control Patients



Data compare measured outcomes of 30-day mortality, 30-day readmissions, and 365-day all-cause mortality in volume-guided subjects and in non–volume-guided propensity-matched control subjects. All comparisons are statistically significant with p values <0.001.

DISCUSSION

This is the first report of clinical and resource use outcomes where direct intravascular volume measurements were used to individualize HF treatment strategy. In this propensity-matched control analysis of a community AHF patient cohort, individualized strategies guided by total blood volume and RBCV measurements resulted in relative reductions of 82% in 30-day mortality, 86% in 365-day mortality rate, and 55% in 30-day readmission rates compared with those of matched control subjects. Although many more subjects than control patients had same-day discharge, LOS overall was 1.7 days longer for volume-guided subjects than for matched control subjects.

The opportunity to optimize HF care by setting treatment strategies and targets in accordance with the measured TBV and RBCV status of each patient appears clinically significant and deserving of further investigation. Clinical assessment and hemodynamic measurements used to infer volume status are surrogate measures of the total blood volume, are often misleading, and cannot quantify volume derangements. Direct measurements of each patient's volume status is a diagnostic tool not an intervention, and the link between its use and improved outcomes requires careful consideration. However, the marked volume heterogeneity observed in this and other studies (8,9) suggests a fundamental physiological rationale for the use of direct blood volume measurement to individualize treatment strategies and improve outcomes on a patient-specific basis.

RBCV status as well as PV status can contribute to volume derangement, and total volume management for patients with anemia or polycythemia should include RBCV correction. Although anemia is a well-established factor indicating poor prognosis in HF (32), its evaluation and management have been problematic in AHF patients (33). Anemia can produce dyspnea and fatigue, symptoms also associated with congestion, and a low Hct in an AHF patient may reflect dilutional anemia due to PV expansion, not true anemia. Importantly, true anemia drives homeostatic, compensatory PV expansion to maintain an adequate TBV. Although 66% of our cohort of patients presenting with signs and symptoms of AHF had excess PV, only 37% were hypervolemic with confirmed excess TBV. Among the 63% of the cohort who were euvolemic or hypovolemic at admission, 4 of 5 had true anemia (122 of 154 subjects). The overall incidence of true anemia, as measured by RBCV, not Hb concentration, was 62%. Both hypervolemia and true anemia were present in 12% of patients. Fully correcting PV excess without concurrently addressing a coexisting RBCV deficit will produce hypovolemia. HF patients are at elevated risk for

TABLE 4 Follow-Up pHct by Anemia and/or Hypervolemia Status

Subject Group	n	LOS	Initial pHct	Follow-up pHct	pHct change	Normalized Hct*	Initial Deficit to Normalized Hct*	Follow-up Deficit to Normalized Hct*
Not anemic, not hypervolemic	32	5.7	40.3	40.6	0.3 ± 2.5	*41.1*	*0.8*	*0.5*
Hypervolemic	62	6.4	36.3	40.9	4.5 ± 3.9	47.4	11.1	6.6
Anemic	122	7.8	32.0	34.8	2.7 ± 2.9	*30.4*	*−1.6*	*−4.4*
Anemic and hypervolemic	29	8.7	28.4	32.9	4.4 ± 2.4	33.8	5.4	0.9

*Normalized Hct (nHct) (defined as the Hct that would result from correcting TBV to Ideal TBV by altering PV only) was used as a decongestion target only for hypervolemic patients; values were calculated, but are shown in *italics* for other subjects.

Hct = hematocrit; pHct = peripheral hematocrit; PV = plasma volume; other abbreviations as in Table 2.

excessive or inappropriate diuresis when true anemia is unrecognized.

In some HF patients, intravascular fluid accumulation may mask polycythemia. Although polycythemia was observed in just 11% of this cohort, previous research using volume quantitation has reported higher incidences in other HF cohorts and an association with poor outcomes (18,23). Like anemia, polycythemia should be considered in volume management.

Although quantitative volume-assessed patients were more likely to be discharged the same day than controls (16.7% vs. 1.4%, respectively), overall LOS was longer for study subjects (7.3 vs. 5.6 days, respectively). Multifactor analysis showed that this increase in LOS was more pronounced among study patients with significant anemia and/or total blood volume excess. The increase in LOS among volume-guided admissions must be contextualized by the reduction in 30-day readmissions. Given current Medicare reimbursement incentives and inpatient management objectives from a cost control perspective, emphasis should be placed on discharging patients as soon as possible and minimizing rehospitalizations (34–37).

The benefit of individualized care guided by BVA appears unrestricted by EF category. Considering the paucity of treatment approaches with proven benefits in HFpEF patients (38), this is a potentially important finding and should direct more definitive research.

STUDY LIMITATIONS. Data were collected from a single community hospital and analyzed retrospectively. CMS data do not include information about specific treatments administered to control patients, nor do they include specific clinical measurements that may be of interest for control subjects (such as EF), so comparison of subjects with controls depends on demographics and comorbidity factors derived from diagnostic codes. Rates of readmission and mortality at 30 days among control patients (27.7% and 11.1%, respectively) were reassuringly comparable to those in CMS 2016 national figures for hospitalized HF (21.6% and 11.9%, respectively) (39,40), suggesting that this cohort was representative of HF admissions in U.S. community practice.

Although rigorous matching mitigates the concern that a selection bias toward healthier patients might have driven the results among study patients, it underscores the need for a prospective multicenter randomized controlled trial to support evidence-based shifts in clinical practice. The cohort size and low overall frequency of negative outcomes suggest caution in interpreting the subset analysis; a larger study may reveal meaningful subset differences in magnitude of benefit and/or outcomes. The primary treatment strategy was individualized and guided by initial BVA results on an ad hoc basis with the consistent goal of normalizing measured TBV and/or RBCV derangement, using a rise in pHct in relation to the patient's nHct as a surrogate marker of interstitial fluid volume decongestion or increase in RBCV, depending on the primary treatment strategy. These results create opportunities to further develop and optimize clear protocols for the evaluation and management of AHF patients through the integration of quantitative blood volume assessment.

CONCLUSIONS

The magnitude of benefit to AHF patients receiving individualized care guided by directly measured intravascular volume status in a large mixed community cohort suggests a path forward to achieving meaningful improvements in clinical and resource use outcomes in patients hospitalized for AHF. This individualized, volume-guided approach merits further study in a randomized controlled trial of volume-guided versus standard-of-care management.

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PERSPECTIVES

COMPETENCY IN CLINICAL KNOWLEDGE: This is the first documentation of the impact on 30-day readmissions, 30-day mortality, and 1-year mortality of integrating directly measured blood volume data into each individual HF patient's decongestion and RBCV correction strategy. Individualization of volume management is necessary to improve the group outcomes because of the extensive heterogeneity of physiologic blood volume disturbances previously documented in cohorts of hospitalized HF patients and the documented inability to accurately assess an individual's total blood volume status based on the use of volume surrogates such as biomarkers, clinical assessment, and hemodynamic assessment.

TRANSLATIONAL OUTLOOK: Achievement of the guideline-based treatment goal, euvolemia, is nearly impossible without direct measurement of blood volume in the HF patient. Accurate assessment and treatment of true anemia in HF patients is difficult without directly measuring RBCV. Finally, the ability to appropriately select patients for treatment with medications selectively benefiting the hypervolemic HF patient is difficult without directly measuring blood volume. These factors combined with more detailed evaluation of the optimal protocols of decongestion and red blood cell volume correction represent fertile areas for future study in the form of prospective randomized clinical trials.

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