Original Paper

Plasma Volume and Renal Function Predict Six-Month Survival after Hospitalization for Acute Decompensated Heart Failure

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Keywords

Heart failure · Mortality · Plasma volume

Abstract

Background: Plasma volume (PV) is contracted in stable patients with heart failure (HF) due to decongestion strategies. On the other hand, increased PV can adversely affect the trajectory of HF. We therefore examined the effects of increased percentage change in PV (%ΔPV), blood urea nitrogen (BUN), and %ΔPV stratified by BUN and glomerular filtration rate (GFR) on survival after discharge in patients hospitalized for acute decompensated HF (ADHF). **Methods:** We used the Strauss-Davis-Rosenbaum formula to calculate the %ΔPV between baseline and hospital discharge in a cohort from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial (ESCAPE). Kaplan-Meier curves were constructed for survival over 6 months. Cox proportional hazards regression was used to obtain adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between survival after discharge and %ΔPV, BUN, and %ΔPV stratified by BUN and GFR. **Results:** Of the 324 patients included in our study (age 56.1 ± 13.6 years, 26.5% female), those with increased or no %ΔPV at discharge were less likely to survive at 6 months compared with those having reduced %ΔPV (log rank, $p = 0.0093$). Increased %ΔPV (HR 1.08 per 10% increase; 95% CI: 1.02–1.14) and increased BUN at discharge (HR 1.02 per mg/dL; 95% CI: 1.01–1.03) were independently associated with worse survival. Decreasing %ΔPV had a great-

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er association with improved survival in patients with discharge BUN <31 mg/dL ($p = 0.02$) and discharge GFR >40 mL/min/1.73 m² ($p = 0.047$). **Conclusions:** Increased %ΔPV and BUN at discharge predicted worse 6-month survival in patients with ADHF. Decreased %ΔPV with low BUN or high GFR at discharge was associated with improved survival.

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Introduction

Plasma volume (PV) is the intravascular portion of the extracellular fluid compartment of the body. PV is generally well regulated in healthy individuals by complex signaling of neuroendocrine systems that maintain water and sodium homeostasis [1]. Any imbalance in the neurohormonal cascade can precipitate detrimental increases in PV in acute decompensated heart failure (ADHF) [2], leading to symptoms of congestion [3] and increased mortality [4–6]. These perturbations in PV may be corrected with diuresis, and the imbalance in the neurohormonal cascade attenuated by inhibitors of the renin-angiotensin-aldosterone system (RAAS).

Changes in PV over time can be calculated indirectly using various equations such as the one described in 1951 by Strauss et al. [7]. The Strauss-Davis-Rosenbaum equation is based on admission and discharge hemoglobin and hematocrit after decongestion during an admission for ADHF. The variables used in the Strauss-Davis-Rosenbaum formula to calculate PV change have independent prognostic implications in chronic systolic heart failure (HF). For instance, anemia in HF is common and is associated with poor outcomes [8, 9], as is hemodilution [10]. There are however other studies reporting conflicting effects of hemoconcentration on survival in HF [11–13].

It is uncertain whether the decrease in PV achieved acutely during an admission for ADHF is associated with improved clinical outcomes, despite the often unavoidable increases in blood urea nitrogen (BUN) or decreases in glomerular filtration rate (GFR). In other words, the beneficial effects of decreased PV with treatment could potentially be outweighed by the negative effects of worsening renal function. We therefore analyzed the ESCAPE database in order to determine the impact of achieving a greater percent decrease in PV (%ΔPV) during therapy for ADHF relative to measures of renal function [14].

Methods

Study Design and Participants

The methods and results of the ESCAPE trial have been previously published [14]. The ESCAPE trial was a prospective randomized controlled trial conducted at 26 sites in the United States and Canada. The trial was designed to determine whether pulmonary artery catheter (PAC) use was safe and if it improved clinical outcomes in patients hospitalized with severe symptomatic and recurrent HF. Between January 2000 and November 2003, the ESCAPE trial enrolled 433 patients hospitalized with severe symptomatic HF, and randomly assigned these patients to receive clinical assessment or PAC-guided therapy. For our study, we included patients from the ESCAPE trial who had complete data on the variables used to calculate PV.

Outcome and Predictor Variables

The main clinical outcome was all-cause mortality after hospital discharge. We used percentage change in PV (%ΔPV) and BUN as predictors of all-cause mortality after hospital discharge.

The Strauss-Davis-Rosenbaum formula was used to calculate the percentage change in PV. The formula is as follows: %ΔPV = $\left[\left(\frac{\text{Hb1}}{\text{Hb2}} \right) \times \left(\frac{(100 - \text{Hct2})}{(100 - \text{Hct1})} \right) - 1 \right] \times 100$, where Hb1 is the hemoglobin at baseline, Hb2 the hemoglobin at discharge, Hct1 the hematocrit at baseline, and Hct2 is the hematocrit at discharge.

Table 1. Baseline characteristics

	Total patients (n = 324)	Patients with increased or no %ΔPV at discharge (n = 157)	Patients with reduced %ΔPV at discharge (n = 167)	p value
Mean age ± SD, years	56.1 ± 13.6	58.7 ± 13.4	53.5 ± 13.2	0.0005
Gender, n (%)				0.501
Male	238 (73.5)	118 (74.2)	120 (71.9)	
Female	86 (26.5)	39 (24.8)	47 (28.1)	
Body mass index	27.9 (24.0–33.0)	28.1 (23.4–32.3)	27.8 (24.2–33.8)	0.5111
Ischemic heart disease, n (%)				0.0180
Yes	177 (54.6)	96 (61.2)	81 (51.5)	
No	145 (44.8)	59 (37.6)	86 (48.5)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Diabetes mellitus, n (%)				0.2170
Yes	112 (34.6)	58 (36.9)	54 (32.3)	
No	210 (64.8)	97 (61.8)	113 (67.7)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Hypertension, n (%)				0.3420
Yes	147 (45.4)	71 (45.2)	76 (45.5)	
No	175 (54.0)	84 (53.5)	91 (54.5)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Chronic obstructive pulmonary disease, n (%)				0.2300
Yes	56 (17.3)	30 (19.1)	26 (15.6)	
No	266 (82.1)	125 (79.6)	141 (84.4)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Stroke, n (%)				0.2500
Yes	29 (9.0)	16 (10.2)	13 (7.8)	
No	293 (90.4)	139 (88.5)	154 (92.2)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Coronary artery bypass graft, n (%)				0.0870
Yes	94 (29.0)	52 (33.1)	42 (25.2)	
No	228 (70.4)	103 (65.6)	125 (74.6)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Atrial fibrillation, n (%)				0.1970
Yes	101 (31.2)	53 (33.8)	48 (28.7)	
No	221 (68.2)	102 (65.0)	119 (71.3)	
Missing	2 (0.6)	2 (1.3)	0 (0.0)	
Blood urea nitrogen, mg/dL	28 (19.0–44.0)	31.5 (23–51)	24 (18–35)	0.0001
Creatinine, mg/dL	1.4 (1.1–1.8)	1.5 (1.1–1.9)	1.3 (1.0–1.7)	0.0036
BUN/creatinine ratio	20.8 (16.7–27.0)	23.1 (17.9–28.8)	19.0 (15.6–24.4)	0.0006

Values are shown as medians (IQR), unless otherwise indicated.

The %ΔPV was used both as a continuous and as a categorical variable, to stratify patients into those with increased or no %ΔPV at hospital discharge (i.e., discharge PV ≥ baseline PV) and those who had reduced %ΔPV at hospital discharge (i.e., discharge PV < baseline PV).

BUN and creatinine (Cr) at discharge were used to estimate renal function. We used BUN both as a continuous and categorical variable to stratify patients into those who had BUN ≤31 and >31 mg/dL at discharge.

Statistical Methods

The analyses were performed in Stata version 14 (Stata Corp., College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). We used age, gender, body mass index, ischemic heart disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, stroke, coronary artery bypass graft surgery, atrial fibrillation, and the BUN to Cr (BUN:Cr) ratio to describe the baseline characteristics of the patients.

We tested BUN thresholds between 30 and 60 mg/dL in increments of 10 mg/dL to define optimal subgroups for the use of PV to predict clinical outcomes. The threshold chosen was the one that defined the subgroup with optimal differentiation of clinical outcomes based on the PV. We also included treatment with medications directed at the RAAS pathway that are associated with improvement in mortality (i.e., ACE inhibitors and beta-blockers). For continuous variables with a normal distribution, the mean and standard deviation were used. For continuous variables with a skewed distribution, the median and interquartile range (IQR) were used. Categorical variables were expressed as numbers with proportions (%). Hypothesis tests with two-sided p values of <0.05 were defined as statistically significant.

For continuous variables, the t test was used to compare baseline means, and the Wilcoxon test was used to compare baseline medians. The χ^2 test was used to compare the proportion of patients with increased or no $\% \Delta PV$ with the proportion of patients with reduced $\% \Delta PV$.

We used Kaplan-Meier (KM) curves to compare 6-month survival for patients who had increased or no $\% \Delta PV$ with patients who had reduced $\% \Delta PV$. In the stratified analysis, the KM curves were stratified by discharge BUN <31 mg/dL, discharge GFR >40 mL/min/1.73 m², and by ACE inhibitors use at discharge.

Bivariable Cox proportional hazards regression was used to obtain hazard ratios (HRs) and 95% confidence intervals (CI) for the association between variables of interest and survival. Variables with p values <0.10 were included in the multivariable Cox proportional hazards analysis used to obtain adjusted HRs and 95% CIs for the associations between survival and $\% \Delta PV$ per 10% increase in PV, as well as between survival and BUN.

Results

Patient Characteristics

Of the 433 patients in the ESCAPE trial, 324 had complete data that allowed calculation of change in PV and were therefore included in our study. Of these 324 patients, 86 (26.5%) were female. The mean age was 56.0 ± 13.5 years (range: 22–88 years). Of these 324 patients, 157 (48.6%) had increased or no $\% \Delta PV$ at discharge, while 167 (51.5%) had reduced $\% \Delta PV$ at discharge (Table 1). In addition, 148 (45.7%) had therapy guided by measurements using a PAC.

Survival and Mortality Outcomes

Of the 324 patients with complete PV data, 60 (18.5%) died after discharge within 6 months of follow-up. Patients who had increased or no $\% \Delta PV$ at discharge were less likely to survive than those who had reduced $\% \Delta PV$ at discharge at the end of the 6-month follow-up period ($p = 0.0093$) (Fig. 1a). However, there were no significant differences in the combined endpoint of death, left ventricular assist device (LVAD) implantation, transplant, and HF rehospitalization between the two groups (Fig. 1b).

Relationship between Reduced PV and Renal Function

The median BUN level in the total population studied was 28.0 mg/dL (IQR, 19.0–44.0 mg/dL), and the corresponding median Cr was 1.4 mg/dL (IQR, 1.1–1.8 mg/dL; Table 1). Patients with increased or no $\% \Delta PV$ at discharge displayed statistically higher BUN and creatinine values relative to those with reduced $\% \Delta PV$ at discharge ($p = 0.0001$ and $p = 0.0036$, respectively) (Table 1). Increased BUN at discharge (HR 1.02 per mg/dL, 95% CI: 1.01–1.02; $p < 0.0001$) and increased creatinine at discharge (HR 1.27 per mg/dL, 95% CI: 1.01–1.46; $p = 0.001$) were both significantly associated with worse survival in bivariable Cox regression models (Table 2).

Increased $\% \Delta PV$ per 10% increase in PV at discharge (HR 1.08, 95% CI: 1.02–1.14; $p = 0.013$) and increased BUN at discharge (HR 1.02 per mg/dL, 95% CI: 1.01–1.03; $p < 0.001$) were both independently associated with worse survival in multivariable Cox regression models, even after adjusting for GFR at discharge (Table 3).

Table 2. Bivariable Cox proportional hazards regression

	Regression coefficient	Standard error	χ^2	<i>p</i> value	Hazard ratio	95% CI lower bound	95% CI upper bound
Change in plasma volume (per 10% increase)	0.0707	0.0271	6.81	0.0091	1.07	1.02	1.13
GFR at discharge	−0.0192	0.0055	12.22	0.0005	0.98	0.97	0.99
Percent change GFR (baseline to discharge)	0.0400	0.365	0.01	0.9123	1.04	0.51	2.13
Creatinine at discharge	0.237	0.072	10.87	0.0010	1.268	1.10	1.46
BUN at discharge	0.0187	0.0041	20.33	<0.0001	1.019	1.01	1.03
PAC-guided strategy	0.153	0.217	0.50	0.480	1.166	0.76	1.78
Ischemic heart disease	0.542	0.228	5.60	0.018	1.719	1.10	2.69
ACE inhibitors at discharge	−0.7449	0.227	10.745	0.001	0.475	0.30	0.74
Beta-blocker at discharge	−0.569	0.218	6.751	0.0094	0.566	0.37	0.87

Fig. 1. Plasma volume change and clinical outcomes. The impact of reduced plasma volume on the outcomes of freedom from death, transplant (Tx), or left ventricular assist device (LVAD) (**a**), and freedom from death, Tx, LVAD, or heart failure rehospitalization (**b**) is shown in the Kaplan-Meier survival curves.

Reduced % Δ PV at discharge showed a greater effect on survival in patients with discharge BUN ≤ 31 mg/dL than in patients with BUN > 31 mg/dL ($p = 0.02$ vs. $p = 0.17$) (Fig. 2a, b). Reduced % Δ PV at discharge also demonstrated a more prominent effect on survival in patients with discharge GFR > 40 mL/min/1.73 m², as compared to patients with GFR ≤ 40 mL/min/1.73 m² ($p = 0.047$ vs. $p = 0.23$) (Fig. 2c, d). There was a weak but significant correlation between increasing % Δ PV and an increase in the percent change in GFR ($r = 0.13$, $p = 0.02$), although not between % Δ PV and final pulmonary capillary wedge pressure (PCWP; $r = 0.15$, $p = 0.12$) in patients randomized to PAC-guided therapy.

Table 3. Multivariable Cox proportional hazards regression

	Regression coefficient	Standard error	χ^2	<i>p</i> value	Adjusted hazard ratio	95% CI lower bound	95% CI upper bound
Change in PV (per 10% increase)	0.074	0.030	6.110	0.013	1.077	1.02	1.14
BUN at discharge	0.016	0.004	12.674	0.000	1.016	1.01	1.03
ACE inhibitors at discharge	−0.615	0.239	6.612	0.010	0.541	0.34	0.86
Beta-blockers at discharge	−0.430	0.227	3.581	0.059	0.651	0.42	1.02

Relationship between Reduced PV and Other Parameters

Reduced % Δ PV at discharge showed a more prominent effect on survival in patients with ischemic heart disease, compared with those having nonischemic HF ($p = 0.008$ vs. $p = 0.55$). In bivariable Cox regression models, ischemic heart disease was also significantly associated with worse survival (HR 1.72, $p = 0.0179$). However, after adjusting for reduced % Δ PV at discharge, BUN at discharge, and GFR at discharge, ischemic heart disease was no longer associated with decreased survival (Table 3).

Both ACE inhibitor and beta-blocker at discharge were independently associated with the outcome of death, transplant, or LVAD after adjustment for the change in PV and BUN at discharge. The p value for the interaction term for ACE inhibitor use at discharge and the change in PV in the model for death, transplant, or LVAD was 0.11.

The effect of reduced % Δ PV was observed in patients who underwent PAC-guided therapy, as opposed to those with therapy guided by clinical assessment alone ($p = 0.005$ vs. $p = 0.37$). As reported in the original trial, randomization to the PAC-guided therapy strategy was not associated with improved survival (HR 1.17, $p = 0.4797$) (Table 2). The survival curves by reduced PV status for patients discharged or not discharged on an ACE inhibitor are also shown (Fig. 2e, f).

Discussion

Our analysis of the ESCAPE cohort compared PV changes along with state of renal function during therapy for ADHF with 6-month clinical outcomes. Patients admitted with ADHF, who displayed a more robust response to diuretic therapy, as indicated by a negative change in PV, had the best outcomes, with the polarity of response noted to be dose-dependent. Changes in PV were not directly correlated with the change in PCWP, suggesting that PV may be an independent parameter for evaluating congestion after therapy for ADHF. This dissociation between volume changes and cardiac filling pressures has previously been reported [15–17] and is partly explained by the fact that greater than two-thirds of the total blood volume is in the venous compartment, which is inherently characterized by high capacitance and less prone to pressure changes [18]. In addition, we noted that PV had the greatest association with outcomes in patients who had a final discharge GFR >40 mL/min/1.73 m² and BUN <31 mg/dL, even though the decrease in PV with therapy was weakly associated with a mild decrease in GFR. These findings are in accordance with a previous analysis by Testani et al. [19] from the same ESCAPE database, demonstrating that aggressive diuresis as measured by hemoconcentration was associated with improved outcomes despite a worsening renal function. The present analysis extends that work by Testani and colleagues by highlighting this critical link of PV changes, renal function, and outcomes during ADHF therapy. In summary, our findings illustrate the importance of noninvasive PV change estimation using

Fig. 2. Plasma volume change and renal function. The differences in survival with and without reduced plasma volume are shown for patients with blood urea nitrogen (BUN) less than the median value (31 mg/dL) (a), BUN greater than or equal to the median (b), glomerular filtration rate (GFR) greater than 40 mL/min/1.73 m² (c), and GFR less than or equal to 40 mL/min/1.73 m² (d), on an angiotensin converting enzyme inhibitor (ACEI) at discharge (e), and not on an ACEI at discharge (f). Tx, transplant; LVAD, left ventricular assist device.

the Strauss-Davis-Rosenbaum formula during ADHF therapy. These results signal the favorability of optimizing decongestion without compromising renal function, as seen in our findings showing improved outcomes among patients achieving a decrease in PV in tandem with BUN <31 mg/dL. In routine clinical practice, however, treating congestion in patients with ADHF while maintaining normal renal function still poses a major clinical challenge even for the most experienced clinicians. Worsening renal function can complicate decongestion strategies. One reason for this clinical conundrum is the heightened activation of the RAAS in the face of decreasing PV [20]. The compensatory mechanisms resulting from the RAAS activation also lead to systemic vasoconstriction and increased left ventricular filling pressures, further straining the already compromised cardiac function.

Patients hospitalized with acute HF are often discharged with persistent signs and symptoms of congestion and/or a high left ventricular filling pressure [21, 22]. It has been shown that decreased congestion, as manifested by hemoconcentration and a decrease in absolute PV, is associated with improved mortality [4–6, 10, 23]. This decrease in PV suggests that diuresis exceeds the rate of plasma refill from the extravascular space and is maintained over the period of decongestive therapy. Hemoconcentration has been associated with worsening of renal function and at the same time also associated with an overall improvement in survival [19]. Of interest, the ADHERE (Acute Decompensated Heart Failure National Registry) risk model identified a significant association between elevated markers of renal dysfunction (BUN and creatinine) and increased in-hospital mortality [24]. On the other hand, hypervolemia is also associated with increased mortality in dialysis-dependent patients [23]. The relationship between PV expansion, renal failure, and increased adverse outcomes is largely mediated by an overactivation of the RAAS. For instance, CHF is a condition that is characterized by PV expansion, which is in part influenced by pronounced activity in the RAAS signaling pathways. Activation of the RAAS leads to systemic vasoconstriction, thereby amplifying renal reabsorption of free water partly through the actions of aldosterone [25]. Conversely, it has also been shown that there is an attenuation of the RAAS activity preceding a reduction in the PV following LVAD implantation [26]. There is however, a paucity of literature about PV changes in response to treatment with HF therapies. The few studies available are characterized by small sample sizes, as well as heterogeneity in study methods of PV measurements and HF disease characteristics (stable vs. acutely decompensated) [27–30].

Of interest, the change in PV was more strongly associated with mortality in the group randomized to treatment with pulmonary artery pressure monitoring, while there was no significant difference in the group randomized to physical assessment-based care. Final pulmonary capillary wedge pressure in the invasive group did not correlate with percent change in PV, which is interesting considering that the ESCAPE trial reported that the routine use of PAC monitoring in advanced HF patients did not confer a mortality benefit [14]. One goal of PAC monitoring is to determine an estimate of left ventricular end diastolic pressure using the PCWP, a primary determinant of left ventricular preload and a surrogate for congestion [31]. This analysis indicates that determining response to therapy by estimating PV changes using an indirect method may compliment the traditional approaches of measuring decongestion with cardiac filling pressure measurements. We recognize the recent observation concerning inadvertent fluid administration in hospitalized patients with HF, and appreciate that an increase in PV could indeed be related to fluid administration, which has been independently associated with complications, increased length of stay, and mortality [32].

While this study raises some interesting findings on the relationship of PV changes and outcomes in HF, more studies are still needed to address the optimal thresholds of PV change during diuretic therapy. For example, defining the optimal PV change during diuretic therapy,

while maintaining adequate renal perfusion and function, could provide practical and meaningful insights for routine clinical use.

Limitations

Although laboratory data were recorded for the vast majority of patients, there was a small incidence of missing laboratory data. In addition, about half of the cohort did not have measured hemodynamic data because they were randomized to conservative therapy. We used the Strauss-Davis-Rosenbaum formula to estimate PV measurements; this method of estimating change in PV has not been validated in the acute HF setting and relies on the assumption that changes in hemoglobin and hematocrit are solely due to changes in PV. Although the follow-up time of 6 months was adequate, the effects of these findings on longer-term outcomes could not be assessed with the available data.

Conclusions

Increased $\% \Delta PV$ and BUN at discharge are predictors of worse 6-month survival for ADHF. Decreased $\% \Delta PV$ with low BUN or high GFR at discharge were associated with improved survival. These findings indicate that among patients who were admitted with ADHF, those that achieved a reduction in PV with preservation of renal function had the best outcomes following discharge.

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Statement of Ethics

All subjects included in this study have given consent according to the protocol of the ESCAPE trial, and no further consent was needed for this analysis. This analysis was approved by the UVA Institutional Review Board for Health Sciences Research.

Disclosure Statement

All authors declare no conflict of interest with this article.

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