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Prognostic value of estimated plasma volume in patients with chronic systolic heart failure

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ABSTRACT

Assessing congestion is challenging but important to patients with chronic heart failure (CHF). However, there are limited data regarding the association between estimated plasma volume status (ePVS) determined using hemoglobin/hematocrit data and outcomes in patients with stable CHF. We prospectively analyzed 231 patients; the median follow-up period was 35.6 months. We calculated ePVS at admission using the Duarte and Strauss formula, derived from hemoglobin and hematocrit ratios and divided patients into three groups. The primary outcome was a composite of all-cause mortality or heart failure rehospitalization. Among 274 patients (61.98 years of age, 2.3% male), the mean ePVS was 3.98±0.90 dL/g. The third ePVS tertile had a higher proportion of primary outcome (71.4%) than the first or second tertile (48.1% and 59.7%, respectively; p=0.013). On multivariable Cox analysis, after adjusting for potential confounders, higher ePVS remained significantly associated with increased rate of primary outcome (adjusted HR 1.567, 95% CI 1.267 to 1.936; p<0.001). Kaplan-Meier survival analyses showed that the occurrence of primary outcome, all-cause mortality and rehospitalization increased progressively from first to third tertiles (p=0.006, 0.014 and 0.001; respectively). In receiver operating characteristic analysis, the area under the curve of ePVS for primary outcome was 0.645. ePVS determined using hemoglobin and hematocrit was independently associated with clinical outcomes for patients with stable CHF. Our study thus further strengthens the evidence that ePVS has important prognostic value in patients with stable CHF.

Trial registration number ChiCTR-ONC-14004463.

Significance of this study

What is already known about this subject?

- Congestion is a major cause of worsening chronic heart failure (CHF). Higher degrees of congestion are associated with higher hospitalization rates and adverse outcomes.
- Estimated plasma volume status (ePVS) derived from the Duarte formula was reported to be a simple and effective clinical examination to measure congestion.
- Limited data regarding the association between ePVS determined using hemoglobin/hematocrit data and outcomes in patients with stable CHF.

What are the new findings?

- ePVS calculated simply from hemoglobin and hematocrit independently provided a predictive value for long-term heart failure hospitalization or mortality outcome in patients with stable systolic CHF.
- ePVS was a better predictor than hemoglobin and hematocrit in the multivariable analysis.

How might these results change the focus of research or clinical practice?

- Hemoglobin and hematocrit to estimate plasma volume (PV) is a low-cost, easily measurable alternative method available in clinical practice. The ePVS measurements may help physicians estimate PV and adjust guideline-based medications on clinical practice in the future.

INTRODUCTION

Chronic heart failure (CHF) is the ultimate pathological outcome of most organic heart disease.[1] Congestion is a major cause of worsening CHF.[2–4] Higher degrees of congestion are associated with higher hospitalization rates and adverse outcomes.[5 6] Relief of congestion is the basic goal of therapy for patients with CHF.[7]

Congestion is difficult to quantify in a non-invasive way, and therefore it is difficult to measure accurately.[3 4] Currently, there are limited means to quantify plasma volume (PV) in patients with CHF. Symptoms and signs can only be used when congestion is apparent.[8] The respective role of congestion scores in routine clinical practice still remains to be determined.[9] Lung ultrasound can capture rapid changes in congestion and may represent the extension of clinical examination in patients.[9] Echocardiographic parameters such as mitral valve E/e′, systolic pulmonary artery pressure and inferior vena cava have some limitations, such as the effect of respiratory status of the patients, need of echocardiography training and presence of different of echocardiographers.[10 11] The radiotracer dilution method is clinically impractical

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and expensive.[12] Daily weight has little effect over longer periods and can only be used when the patient's 'dry weight' is known.[13] Additional objective measures of congestion consistent with simple and effective clinical examinations may be helpful.[14 15]

It has been shown that estimated PV status (ePVS) which is calculated from weight and hematocrit, was associated with prognosis in CHF cohorts.[15] Nevertheless, the dry weight is difficult to measure and agreement between the calculated and measured PV levels in this cohort was appraised only in male patients with CHF.[13 15] ePVS derived from hemoglobin and hematocrit may represent a better tool to reflect congestion. ePVS estimated from the Duarte formula was reported to be associated with clinical outcomes in patients with heart failure with preserved ejection fraction (EF).[16 17] Nevertheless, despite the published data on the ePVS estimated from the Duarte formula in patients with CHF,[18] the contribution of ePVS to the clinical outcomes of patients with stable systolic CHF has not been sufficiently investigated. Moreover, as patients with CHF spend most of their time self-managing outside the hospital,[19] simple and reliable PV monitoring is more meaningful for patients with stable CHF rather than hospitalized patients with CHF.[15] Therefore, we investigated ePVS using hemoglobin and hematocrit and outcomes in patients with stable systolic CHF in the present study.

MATERIAL AND METHODS

Study populations

This was a prospective cohort study. We recruited patients diagnosed with systolic heart failure (HF) according to the '2014 China Heart Failure Diagnosis and Treatment Guideline' and '2012 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure'[20] in Xunyi Hospital and Jingyang Hospital in Shaanxi, China, before and treated in the outpatient clinics from 2014 to 2015. Inclusion criteria were as follows: age 18–80 years; echocardiography showing left ventricular ejection fraction (LVEF) of <50%; not hospitalized in the past month. All patients were included after the stabilization of both clinical status and medications. According to the guidelines, patients were administered standardized drug treatment regimens[20] to reduce deviations in patient treatment regimens arising from different medical units and physicians. The ePVS data in this prospective study were not used for treatment decisions. Hypertension was defined as systolic blood pressure (BP) of ≥140 mm Hg, diastolic BP of ≥90 mm Hg, or use of at least one class of antihypertensive agents.[21] We defined non-insulin-dependent diabetes mellitus as fasting blood glucose concentration of >126 mg/dL and/or use of at least one oral hypoglycemic agent.[22] Atrial fibrillation was defined according to '2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation'.[23] Anemia was defined according to the WHO criteria as a baseline hemoglobin of <130 g/L for men and <120 g/L for women.

The exclusion criteria were as follows: CHF related to congenital heart diseases, valvular disease or pericardial disease, acute HF, chronic obstructive pulmonary disease or life-threatening malignancy, pregnancy and lactation, and dementia or mental disorders. Note that patients with clinically significant bleeding events were excluded because either transfusion therapy or blood loss would change hemoglobin level, thereby affecting the calculation of ePVS.

Clinical measurement

We recorded physical and clinical characteristics, medical histories, blood chemistry data and medications at admission. Body mass index (BMI) was determined according to weight in kilogram divided by the square of height in meter (kg/m^2).[24] Estimated glomerular filtration rate was assessed using the Modification of Diet in Renal Disease 4 variable formula.[25] We calculated the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) scores of all subjects to fit the multivariable Cox regression model.[26]

Estimated plasma volume status (ePVS) in this study was calculated from the Strauss-derived Duarte formula using hemoglobin and hematocrit values as follows[14]: ePVS=(100−hematocrit (%))/hemoglobin (g/L).

Outcomes and follow-up

The primary outcome was a composite of all-cause mortality or rehospitalization due to worsening HF. The median follow-up period was 35.6 months, and the longest follow-up period was 43 months. Recording study endpoint information was documented via telephone interviews, by regular outpatient follow-up, or by electronic hospital records.

Statistical analysis

The Kolmogorov-Smirnov test was used to test normal distribution of continuous variables. Normally distributed variables are expressed as mean±SD, and median value (25th–75th IQR) for non-normally distributed continuous variables. The frequency of categorical variables is expressed as numbers (n) (percentages (%)). As the distribution of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels had a skewed distribution, it was normalized with logarithmic transformation (abbreviated as logBNP). The comparisons between ePVS tertile groups showing normal distribution were made using the Student t-test or otherwise by the Mann-Whitney U test. We used the Pearson χ^2 test to compare categorical data. Correlational statistics (Pearson's rho) between ePVS, logBNP, and LVEF were computed. Correlations of r/rho=0.25 or greater (absolute value) were noted and p values were reported. Cox regression analyses were performed to evaluate the associations between ePVS and outcomes. Univariable analyses were used for most baseline variables to find variables that might be associated with primary outcome. Next, all variables that showed a significant ($p<0.10$) univariate association and which were known to be significant for predicting primary outcome in patients with HF were included in a multivariable model. The multivariate analysis included age, gender, systolic BP, MAGGIC score, logBNP, ePVS, hemoglobin, hematocrit and LVEF. We used 'forward selection' to ensure that variables that did not retain significance ($p>0.10$) in this multivariable analyses were not added to the final model. Moreover, any variable highly correlated with another variable and with a less significant p value was not retained. Cox analyses were used to evaluate the survival, while the Harrel concordance index (C-index) was used to testify

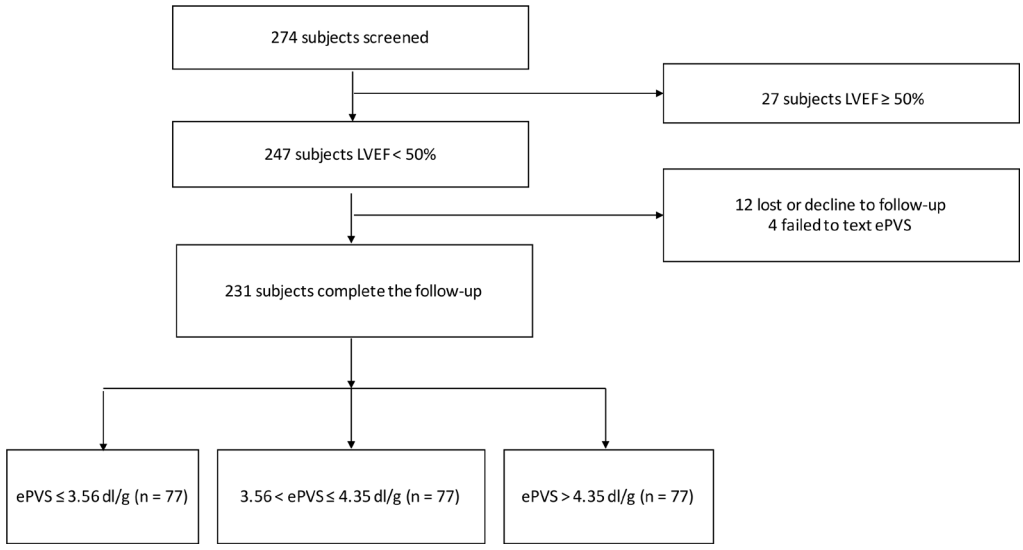

Figure 1 Flowchart of enrollment and follow-up of study cohort. ePVS, estimated plasma volume status; LVEF, left ventricular ejection fraction.

the predictive accuracy for each model. Receiver operating characteristic (ROC) curve analyses were performed to calculate areas under the curve (AUCs). Survival probabilities were estimated using the Kaplan-Meier method and were plotted as survival curves, which were compared using the log-rank test. Subgroup analyses were performed using univariable Cox regression analyses for primary outcome: reduced and mid-range LVEF. As the patient may die before rehospitalization, the assumption that censored observations have the same rehospitalization hazard as those at risk is not fulfilled; therefore, we performed competing-risk survival regression analysis for rehospitalization. The interaction between ePVS and anemia for primary outcome was tested using two-way analysis of variance. A p value of <0.05 (two-tailed) was considered significant. Statistical analyses and graphing were performed using the IBM SPSS Statistics V.21.0, STATA V.13.1 and GraphPad Prism V.5.0 (GraphPad Software, Cary, North Carolina, USA).

RESULTS

Baseline characteristic

Overall, 274 patients were included. Of these, 27 had an EF of ≥50%, and 12 were lost to follow-up or declined to continue. The vital status could not be assessed in four patients. The remaining 231 patients comprised the study group. The cohort was respectively categorized according to ePVS tertiles: lower tertile—ePVS≤3.56 dL/g, middle tertile—3.56<ePVS≤4.35 dL/g, and upper tertile—ePVS>4.35 dL/g. A flowchart for the inclusion and follow-up algorithms is shown in figure 1. After a median follow-up period of 35.6 months, 138 patients (59.7%) experienced the primary outcome, including 60 who died (26%) and 122 who were rehospitalized for HF (52.8%). Characteristics of the study population are shown in online supplemental table S1.

Factors associated with estimated PV at baseline

The average age in the study was 61.98±9.11 years and 62.3% were male (table 1). Patients with higher ePVS were more likely to be female, older and to have lower weights and BMIs. In addition, the uric acid, creatinine, hemoglobin, and hematocrit concentrations were significantly lower, while New York Heart Association (NYHA) classes were higher. The NT-proBNP was significantly different between the three groups (1602, 2726, and 3035 pg/mL for the first, second, and third ePVS tertiles, respectively; p=0.001). There were no significant differences between the three groups with respect to medications use. Most medical history features and laboratory values were comparable among the groups (table 1).

ePVS and outcomes

In the univariable Cox regression analyses, higher ePVS values were significantly associated with increased rates of the primary outcome (HR 1.659, 95% CI 1.358 to 2.027; p<0.001) (online supplemental table S3). After adjusting for MAGGIC score and logBNP, ePVS remained an independent predictor of primary outcome (adjusted HR 1.567, 95% CI 1.267 to 1.936; p<0.001) (table 2). To test the statistical concordance, we used the Harrel C-index to quantify the predictive accuracy of the multivariate models (table 2). For a multivariate Cox model with ePVS as independent variable, the C-index was 0.618. When adding the MAGGIC score, this value increased to 0.646. However, the C-index rose to 0.659 when adding logBNP to variables. Finally, when both the MAGGIC score and logBNP were added to the model, the C-index rose to 0.662, and the concordance of the model was higher than the original model that included only ePVS. Moreover, when taking competing risks into account, ePVS remained a predictor of HF rehospitalization (online supplemental figure S5).

No significant correlation was found between ePVS and LVEF (Pearson correlation=−0.008, p=0.903), while weak correlations were found among logBNP, ePVS and logBNP, and LEVF (online supplemental table S2). In the multivariable Cox regression analysis for primary outcome, the variations in individual hemoglobin and hematocrit values were not retained because of the expected correlations with ePVS

Table 1 Overall patient characteristics according to ePVS tertiles

Clinical characteristics	Total (N=231)	First (ePVS≤3.56 dL/g) (n=77)	Second (3.56<ePVS≤4.35 dL/g) (n=77)	Third (ePVS>4.35 dL/g) (n=77)	P value
Clinical variables					
Age (years)	61.98±9.11	59.30±8.74	63.58±8.86	63.04±9.21	0.006
Male (%)	62.3, n=144	90.9, n=70	61.0, n=47	35.1, n=27	<0.001
Smoking (%)	52.4, n=121	80.5, n=62	49.4, n=38	27.3, n=21	<0.001
Alcohol consumption (%)	41.1, n=95	55.8, n=43	39.0, n=30	28.6, n=22	0.002
Medical history (%)					
Hypertension	30.3, n=70	33.8, n=26	32.5, n=25	24.7, n=19	0.414
Coronary artery disease	36.8, n=85	46.8, n=36	36.4, n=28	27.3, n=21	0.043
Diabetes mellitus	8.7, n=20	6.5, n=5	10.4, n=8	9.1, n=7	0.682
Atrial fibrillation	7.8, n=18	9.1, n=7	9.1, n=7	5.2, n=4	0.581
Symptoms and physical examination					
NYHA functional class (%)					
I	18.3	26.0	18.2	10.5	0.172
II	57.0	53.2	57.1	60.5	
III	24.8	20.8	24.7	28.9	
Lung rales (%)	16.0%, n=37	18.2%, n=14	7.8%, n=6	22.1%, n=17	0.113
Third heart sound (%)	27.7%, n=64	28.6%, n=22	24.7%, n=19	29.9%, n=23	0.349
Peripheral edema (%)	20.8%, n=48	16.9%, n=13	24.7%, n=19	20.8%, n=16	0.238
Systolic BP (mm Hg)	121.41±21.12	122.42±21.23	125.06±20.73	116.74±20.80	0.044
Diastolic BP (mm Hg)	76.11±11.34	78.06±10.82	78.01±11.73	72.25±10.58	0.001
Heart rate (beats/min)	77.79±16.31	79.68±15.53	76.13±16.11	77.56±17.25	0.400
Weight (kg)	59.81±11.55	65.74±11.96	58.96±10.72	54.73±9.11	<0.001
BMI (kg/m^2)	23.06±3.75	24.30±4.06	23.01±3.50	21.86±3.30	<0.001
MAGGIC score	17.35±5.36	15.78±4.74	18.24±5.43	18.04±5.58	0.007
NT-proBNP (pg/mL)	2454±171	1602±193	2726±338	3035±313	0.001
ePVS	3.98±0.90	3.05±0.46	3.92±0.21	4.97±0.54	<0.001
Laboratory values					
Sodium (mmol/L)	140.23±2.87	140.34±3.14	140.14±2.31	140.21±3.11	0.909
Potassium (mmol/L)	4.34±0.46	4.31±0.50	4.34±0.49	4.37±0.40	0.749
Albumin (g/dL)	4.27±0.34	4.33±0.35	4.27±0.37	4.21±0.29	0.089
Uric acid (mg/dL)	326.32±88.09	355.79±76.99	322.81±92.41	300.35±86.27	<0.001
BUN (mg/dL)	19.12±5.12	18.81±5.51	19.51±4.30	19.06±5.46	0.804
Creatinine (mg/dL)	0.78±0.17	0.81±0.18	0.78±0.16	0.74±0.17	0.021
eGFR (mL/min/1.73 m^2)	86.53±18.94	90.37±18.40	85.18±19.87	84.03±18.13	0.086
Hemoglobin (g/L)	146.5±19.7	166.9±14.8	145.7±05.9	126.9±10.2	<0.001
Hematocrit (%)	43.33±6.23	49.63±5.17	43.01±2.24	37.36±3.07	<0.001
Echocardiography					
LVEF (%)	35.75±7.65	35.94±7.61	35.11±7.59	36.19±7.81	0.658
LVEDD (mm)	69.06±8.79	69.13±8.76	70.27±8.78	67.79±8.79	0.216
LVESD (mm)	56.49±9.06	56.53±8.92	57.79±8.78	55.16±9.40	0.196
E wave (m/s)	0.76±0.05	0.75±0.04	0.77±0.05	0.75±0.04	0.940
A wave (m/s)	0.73±0.02	0.76±0.04	0.78±0.04	0.67±0.04	0.112
E:A ratio	1.25±0.07	1.21±0.12	1.14±0.11	1.39±0.13	0.339
Medications					
ACEI/ARB (%)	88.7%, n=205	92.2%, n=71	90.9%, n=70	83.1%, n=64	0.105
Beta blocker (%)	81.4%, n=188	87.0%, n=67	77.9%, n=60	79.2%, n=61	0.293
Aldosterone antagonist (%)	77.5%, n=179	79.2%, n=61	76.6%, n=59	76.6%, n=59	0.905
Diuretics (%)	56.3%, n=130	54.5%, n=42	55.8%, n=43	58.4%, n=45	0.884
Digitalis (%)	21.6%, n=50	18.2%, n=14	27.3%, n=21	19.5%, n=15	0.334
Coenzyme Q10 (%)	12.1%, n=28	12.9%, n=10	7.8%, n=6	15.6%, n=12	0.410

Values are mean±SD, n (%) or median (25th–75th percentile).
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, pro-brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ePVS, estimated plasma volume status; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide.

(Pearson correlation=−0.954 for hemoglobin variation, Pearson correlation=−0.923 for hematocrit variation) and with a less significant p value (table 3). ePVS was a better predictor of primary outcome than hemoglobin and hematocrit. Of note, in the subgroup analyses of both reduced and mid-range LVEF, higher ePVS values were also associated

Table 2 Multivariable Cox regression analyses for primary outcome

Model	HR (95% CI) for ePVS	P value	C-index
ePVS crude HR	1.659 (1.358 to 2.027)	<0.001	0.618
Model 1 ePVS+age+gender	1.659 (1.358 to 2.027)	<0.001	0.616
Model 2 ePVS+MAGGIC score	1.637 (1.333 to 2.011)	<0.001	0.646
Model 3 ePVS+logBNP	1.552 (1.258 to 1.914)	<0.001	0.659
Model 4 ePVS+MAGGIC score+logBNP	1.567 (1.267 to 1.936)	<0.001	0.662

Multivariable analysis results are reported for model 1, which included variables ePVS, age and gender. Multivariable model 2 included variables ePVS and MAGGIC score. Multivariable model 3 included variables ePVS and logBNP. Multivariable model 4 included variables ePVS, MAGGIC score and logBNP.
BNP, pro-brain natriuretic peptide; ePVS, estimated plasma volume status; LVEF, left ventricular ejection fraction; MAGGIC score, Meta-analysis Global Group in Chronic Heart Failure; logBNP, normalized BNP with logarithmic transformation.

Table 3 Multivariable Cox regression analysis for primary outcome

Variables retained by the model	HR (95% CI)	P value
ePVS	1.554 (1.263 to 1.914)	<0.001
logBNP	1.747 (1.140 to 2.676)	0.010
LVEF	0.966 (0.945 to 0.987)	0.002

ePVS was retained in the Cox regression analysis model (HR: 1.554, 95% CI 1.263 to 1.914; p<0.001). Variables: age, gender, systolic BP, MAGGIC score, logBNP, ePVS, hemoglobin, hematocrit and LVEF.
BNP, pro-brain natriuretic peptide; BP, blood pressure; ePVS, estimated plasma volume status; logBNP, normalized BNP with logarithmic transformation.LVEF, left ventricular ejection fraction; MAGGIC score, Meta-analysis Global Group in Chronic Heart Failure;

with increased rates of the primary outcome (online supplemental table S4). Furthermore, as shown in online supplemental table S6, there was no interactive effect of ePVS and anemia on primary outcome (p interaction=0.275).

ePVS (AUC=0.645) and logBNP (AUC=0.692) were both good predictors of primary outcome (figure 2A). Similarly, for all-cause death, ePVS (AUC=0.638) and logBNP (AUC=0.711) were also good predictors (figure 2B). Analysis for HF rehospitalization, ePVS (AUC=0.647) and logBNP (AUC=0.648) were also good predictors (figure 2C). To further explore the importance of measuring ePVS at the time of clinical follow-up, Kaplan-Meier survival analysis was performed with ePVS tertiles. Kaplan-Meier estimates of the primary outcome stratified by ePVS tertiles showed that patients with CHF with higher baseline ePVS were predisposed to a greater risk of primary outcome (log-rank test: p=0.006). The curve is shown in figure 3A. A similar trend was observed between ePVS and all-cause death (log-rank test: p=0.014) (figure 3B). Analysis of HF rehospitalization was also significant for log-rank test (p=0.001) (figure 3C).

DISCUSSION

Using a long follow-up prospective CHF cohort, we found that ePVS derived from hemoglobin and hematocrit predicted HF hospitalization or mortality events independently of major variables. This formula includes both hemoglobin and hematocrit, which may be relevant in patients with HF with cardiorenal anemia syndrome.[27] Although both hematocrit and hemoglobin were associated with outcomes under univariate analyses, ePVS was a better predictor than hemoglobin and hematocrit in the multivariable analysis due to the collinearity with ePVS and with a less significant p value.

Daily body weights reflect daily fluctuations in PV, but this is insufficiently informative over a longer period and only accurate when the patient's dry weight is known.[13] In addition, body weight loss, which was found to be related to worse outcomes, may rather be related to cachexia as opposed to decongestion and therefore may be misleading for use in monitoring congestive status.[13] In our study, there was a trend that patients with higher ePVS had severe clinical signs and symptoms of congestion. NYHA classes were higher when patients had higher ePVS, although there was no significant difference. For lung rales and edema, the trend was not consistent. Many factors can affect the symptoms and signs of patients with CHF; congestion is one of the factors.[8] Symptoms and signs can only be used to quantify PV when congestion is apparent.[8] The correlation between vascular volume and clinical symptoms and signs is complex and requires further exploration.

An analysis reported that ePVS was associated with invasively measured left ventricular end-diastolic pressure,[28] whereas ePVS was preferably associated with left-sided hemodynamic markers of congestion.[28] These results indicate that ePVS is a congestion variable rather than a

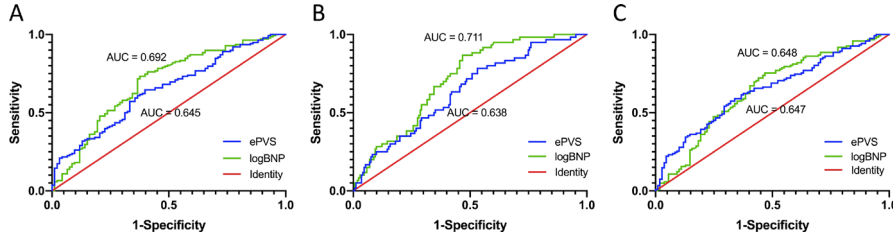

Figure 2 ROC curves related to NT-proBNP and ePVS. ROC curves for logBNP (AUC=0.692) and ePVS (AUC=0.645) measurements. Relation of ePVS and logBNP to primary outcome (A). ROC curves related to logBNP (AUC=0.711) and ePVS (AUC=0.638) for all-cause death (B). ROC curves related to logBNP (AUC=0.648) and ePVS (AUC=0.647) for rehospitalization (C). AUC, area under the curve; BNP, brain natriuretic peptide; ePVS, estimated plasma volume status; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic.

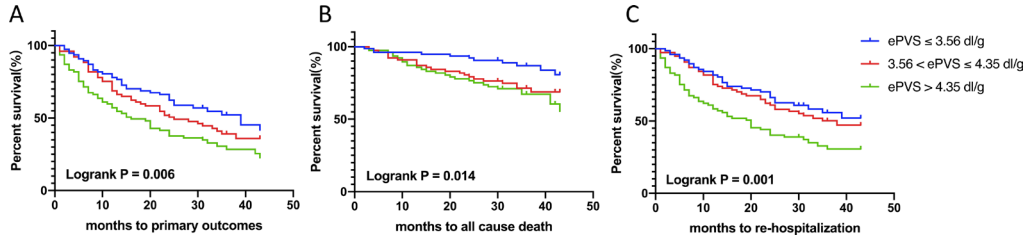

Figure 3 Kaplan-Meier survival curves according to ePVS tertiles. Kaplan-Meier curves for patients were divided into tertiles of ePVS from baseline to the end of the follow-up. Relation of ePVS to primary outcome (A), all-cause death (B) and rehospitalization (C). ePVS, estimated plasma volume status.

comorbidity variable. In addition to traditional routine clinical assessments, this ePVS method allows physicians to assess a patient's congestive status and to predict future prognosis.

PV estimation is important in the management of patients with HF to tailor diuretic doses to the needs of the individual patient, but is often not achieved due to the unreliability of clinical signs and symptoms.[29] The ePVS measurements may help physicians estimate PV and adjust guideline-based medications. Patients with HF are not always able to undergo outpatient clinic treatment, medication, or follow-up in centers with various biomarkers laboratory tests.[30] In these situations, hemoglobin and hematocrit to estimate PV is a low-cost, easily measurable alternative method available in clinical practice.

Our study had some limitations. First, our study was an observational cohort, with the usual limitations of such protocols. Second, although we found that the ePVS showed a consistent trend in predicting the outcomes at the end of the follow-up period, we believe that we have not been able to obtain the variation of ePVS over time. Using more time series may be more clinically significant and predictive to replace a single test with a baseline test. Third, we included only two centers. The number of patients in the cohort was relatively small. Although we obtained long-term independent forecast values, the overall power was not high. Prospective cohort studies with larger sample sizes in the future can provide more reliable evidence. Finally, the therapy associated results presented here are largely hypothetical. Therefore, prospective studies are required to fully evaluate the therapy-associated potential of ePVS. Despite these limitations, we believe that our research has potential clinical implications. Our study further strengthens the evidence for an important prognostic value of ePVS in patients with stable systolic CHF.

CONCLUSION

In summary, ePVS calculated simply from hemoglobin and hematocrit independently provided a predictive value for long-term HF hospitalization or mortality outcome in patients with stable systolic CHF.

Contributors YL: methodology, writing and original draft preparation; YX: supervision and investigation; JL: data curation and investigation; XW: validation and investigation; LW: data curation; JL: investigation; LB: supervision, writing, reviewing and editing the manuscript; AM: conceptualization, writing, reviewing and editing.

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Competing interests None declared.

Patient consent for publication Not required.

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