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Short Communication

Estimated Plasma Volume Status (ePVS) for Diastolic Heart Failure in the Intensive Care Unit: A Retrospective Cohort Study

Jun Chen[2], Qiang Liu[1,2*]

[1]The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310000, China

[2]The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310000, China

*Correspondence should be addressed to Qiang Liu, 199810111@zcmu.edu.cn

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Diastolic heart failure (DHF) is also be regarded as heart failure with preserved ejection fraction (HFpEF), is estimated to occur in 40 to 50% of patients with HF [1]. More than 70% of HF patients over the age of 65 had HFpEF, and the incidence and prevalence of HFpEF has been increased by 10% every 10 years in comparison to HF with reduced ejection fraction (HFrEF), and this gap is expected to widen in the coming years [2]. Compared with HFrEF, cardiac congestion in HFpEF is more difficult to evaluate non-invasively, thus, fluid volume evaluation and management remained a challenge for patients with DHF in the intensive care unit (ICU).

Direct quantification of plasma volume was of great clinical application value in revealing volume overload severity in chronic HF patients, however, this methodology is difficult to obtain for clinicians [3]. Estimate plasma volume status (ePVS) is a good substitute for the evaluation of plasma volume status. Recently, ePVS derived from Duarte formula has been widely reported as a predictor for decompensated HF [4,5]. However, there are limited studies for ePVS in the DHF patients, especially the patients in the ICU with DHF, thus, the clinical application value of ePVS for the DHF patients in the ICU also needs to be further explored. Given that plasma volume status have great value in the subsequent fluid treatment of HF patients during hospitalization, we aimed to determine whether high levels of plasma volume status derived from formulas (Duarte formula, Hakim formula, or Kaplan formula) were associated with poor prognosis of the ICU patients with DHF, and to provide more fluid volume status reference for the ICU patients with DHF.

Adult patients (aged >18 years old) admitted to the ICU and diagnosed with DHF (ICD-9 diagnosis codes "4275" and ICD-10 diagnosis codes "I46", "I462", "I468", "I469") were enrolled in our study. Their information (general characteristics, vital sign data, laboratory tests data, therapy, APSII and SOFA score) were extracted from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database.

The ePVS calculated by Duarte formula as:

ePVS.Duarte = 100 × (1-hematocrit)/hemoglobin (g/dL) [6].

The ePVS derived from Hakim formula as:

Actual plasma volume: (1-hematocrit)×(a+b×body weight in kg). Ideal plasma volume = c×body weight in kg. ePVS.Hakim = [(actual plasma volume-ideal plasma volume)/ideal plasma volume]×100 (males: a = 1530, b = 41.0, c = 39; females; a = 864, b = 47.9, c = 40) [6].

The ePVS derived from Kaplan formula was similar to the ePVS derived from Hakim formula without gender distinguishment which calculated as:

ePVS.Kaplan = 0.065 × body weight × (1-hematocrit) × 1000 [7].

Continuous variables conforming to normal distribution were expressed as the mean ± standard deviation (SD). Continuous variables conforming to skewness distribution were expressed as medians with upper and lower quartiles. Categorical variables were expressed as frequencies with percentages. The t-test or Wilcoxon rank-sum test were performed for groups comparison with continuous variables, and the chi-square test or Fisher's exact test were performed for categorical variables groups comparison. Multivariate Cox proportional risk regression model was used to pool the hazard ratio (HR) of ePVS. All tests were 2-tailed tests, and p ≤ 0.05 was represented as statistically significant. Statistical analyses were performed using R version 3.6.3.

A total of 10,238 eligible patients (age 74.69 ± 12.80 years old, males 45.30%) were included in our study. 1,253 patients (12.24%) died in the hospital. The baseline characteristics of DHF patients were summarized in **Table 1**. The average age in the survival group was 74.18 ± 12.92 years old and in the death group was 78.34 ± 11.34 years old (P<0.001). The death

Table 1: The characteristic of included subjects.

Characteristic	Total (n=10238)	Survival (n=8985)	Death (n=1253)	P value
Age (years old)	74.69 ± 12.80	74.18 ± 12.92	78.34 ± 11.34	**<0.001**
Man	4634 (45.30%)	4062 (45.20%)	572 (45.70%)	0.792
Weight	84.19 ± 27.31	84.94 ± 27.44	78.85 ± 25.77	**<0.001**
SBP (mmHg)	118.69 ± 17.42	118.71 ± 17.45	118.51 ± 17.28	0.696
DBP (mmHg)	61.31 ± 11.36	61.30 ± 11.42	61.43 ± 10.92	0.685
MBP (mmHg)	76.86 ± 11.08	76.84 ± 11.11	76.99 ± 10.83	0.641
Heart rate (beats/minute)	83.96 ± 16.24	83.92 ± 16.32	84.25 ± 15.61	0.498
Respiratory rate (beats/minute)	20.13 ± 3.79	20.11 ± 3.77	20.28 ± 3.91	0.143
Temperature (°C)	36.78 ± 0.46	36.78 ± 0.46	36.79 ± 0.49	0.859
SPO2 (%)	96.28 ± 2.35	96.27 ± 2.34	96.32 ± 2.43	0.498
Diabetes	4490 (43.90%)	4011 (44.60%)	479 (38.20%)	**<0.001**
myocardial infarction	2477 (24.20%)	2147 (23.90%)	330 (26.30%)	0.064
Chronic pulmonary disease	4451 (43.50%)	3924 (43.70%)	527 (42.10%)	0.294
Renal disease	3655 (35.70%)	3145 (35.00%)	510 (40.70%)	**<0.001**
Anion gap (mEq/L)	15.03 ± 3.92	15.02 ± 3.89	15.10 ± 4.10	0.494
BUN (mg/dL)	34.43 ± 24.00	34.38 ± 23.89	34.80 ± 24.78	0.555
Bicarbonate (mmol/L)	24.72 ± 5.66	24.77 ± 5.69	24.39 ± 5.44	**0.026**
Creatinine (mg/dL)	1.74 ± 1.59	1.74 ± 1.59	1.77 ± 1.62	0.533
Chloride (mmol/L)	101.16 ± 7.14	101.11 ± 7.25	101.48 ± 6.30	0.091
Hematocrit (%)	31.84 ± 6.20	31.95 ± 6.20	34.28 ± 0.34	**<0.001**
Hemoglobin (g/dL)	10.18 ± 2.05	10.24 ± 2.05	11.18 ± 0.12	**<0.001**
ePVS.Duarte	7.09 ± 2.01	7.03 ± 1.99	7.45 ± 2.10	**<0.001**
ePVS.Hakim	2.69 ± 12.21	2.30 ± 12.18	5.50 ± 12.06	**<0.001**
ePVS.Kaplan	3715.32 ± 1195.00	3740.95 ± 1194.35	3531.53 ± 1184.00	**<0.001**
Potassium (mmol/L)	4.36 ± 0.68	4.36 ± 0.68	4.40 ± 0.69	0.063
Sodium (mmol/L)	138.22 ± 6.53	138.19 ± 6.75	138.39 ± 4.72	0.314
SOFA	5.21 ± 3.45	5.16 ± 3.41	5.54 ± 3.68	**<0.001**
SAPSII	39.53 ± 12.78	39.46 ± 12.78	39.97 ± 12.71	0.184
APSIII	51.08 ± 21.41	51.01 ± 21.43	51.55 ± 21.30	0.398
ICU LOS, days	3.65 ± 4.68	3.41 ± 4.32	5.39 ± 6.49	**<0.001**
HOS LOS (days)	11.91 ± 12.64	11.78 ± 12.31	12.81 ± 14.78	**<0.001**
HOS mortality, n (%)	1253 (12.24%)	0 (0%)	1253 (100%)	**NA**

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MBP: Mean Blood Pressure; SPO2: Pulse Oximetry Derived Oxygen Saturation; BUN: Blood Urea Nitrogen; INR: International Nominal Ratio; WBC: White Blood Cell; SOFA: Sequential Organ Failure Assessment; APSII: Acute Physiology Score II; ICU: Intensive Care Unit; HOS: Hospital; LOS: Length Of Stay.

Table 2: Multivariable Cox analysis of risk factors.

variable	ePVS.Duarte		ePVS.Hakim		ePVS.Kaplan	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years old)	1.036 (1.031-1.042)	<0.001	1.037 (1.031-1.042)	<0.001	1.036 (1.030-1.042)	<0.001
Weight (kg)	0.995 (0.992-0.997)	<0.001	1.000 (0.996-1.005)	0.900	0.983 (0.960-1.007)	0.154
Bicarbonate	0.992 (0.982-1.002)	0.114	0.992 (0.982-1.002)	0.123	0.992 (0.982-1.002)	0.115
Hematocrit (%)	1.149 (1.110-1.189)	<0.001	1.173 (1.129-1.219)	<0.001	1.156 (1.106-1.208)	<0.001
Hemoglobin (g/L)	0.738 (0.652-0.836)	<0.001	0.691 (0.625-0.764)	<0.001	0.690 (0.623-0.763)	0.005
Renal disease (%)	1.139 (1.013-1.281)	0.030	1.147 (1.020-1.290)	0.022	1.137 (1.011-1.278)	0.032
Diabetes (%)	0.851 (0.755-0.960)	0.009	0.855 (0.758-0.965)	0.011	0.849 (0.753-0.957)	0.008
ePVS.Duarte	1.101 (0.991-1.224)	0.074	-	NA	-	NA
ePVS.Hakim	-	NA	1.021 (1.007-1.035)	0.003	-	NA
ePVS.Kaplan	-	NA	-	NA	1.000 (1.000-1.001)	0.306
SOFA Score	1.022 (1.006-1.038)	0.008	1.022 (1.006-1.038)	0.008	1.022 (1.006-1.038)	0.008

HR: Hazard Ratio; BMI: body mass index; PP: Pulse Pressure (systolic blood pressure minus diastolic blood pressure); UA: Uric Acid; HDL-C: High Density Lipoprotein-C; LP(a): Lipoprotein(a); HbA1c: Glycosylated Hemoglobin; Mg: Serum Magnesium.

group patients presented with higher level of hematocrit and hemoglobin, as well as higher SOFA scores. Multivariable Cox proportional risk regression analysis results determined age (HR: 1.036; 95% CI: 1.031-1.042, P<0.001), hematocrit (HR: 1.149; 95% CI: 1.110-1.189, P<0.001), hemoglobin (HR: 0.738; 95% CI: 0.652-0.836, P<0.001), renal disease (HR: 1.139; 95% CI: 1.013-1.281, P=0.030), diabetes (HR: 0.851; 95% CI: 0.755-0.960, P=0.009), SOFA Score (HR: 1.022; 95% CI: 1.006-1.038, P=0.008), and ePVS.Hakim (HR: 1.021; 95% CI: 1.007-1.035, P=0.003) as the independent risk factors for the in-hospital death of patients with DHF in the ICU (**Table 2**).

As an indicator of circulatory congestion, the clinical utility of ePVS has been demonstrated in previous clinical researches [4,5,8,9]. There are several available formulas for ePVS's calculation. EPVS derived from Hakim formula and ePVS derived from Duarte formula are the most commonly used formulas currently. In our study, we confirmed that higher plasma volume is closely associated with adverse in-hospital clinical outcome, and ePVS derived from Hakim formula is proved to be an independent risk factor for in-hospital death in patients with DHF. Of note, in our research, ePVS derived from Duarte formula did not demonstrate a statistical difference in multivariable Cox regression analysis, and the ePVS derived from Kaplan formula almost has no clinical application value (as seen in **Table 2**). Compared with ePVS derived from Duarte formula, ePVS derived from Hakim formula was more reasonable and accuracy, which considering the effect of gender and weight, that was the reason why ePVS derived from Hakim formula was superior to ePVS derived from Duarte in evaluating the clinical outcome of patients with DHF in the ICU. For the DHF patients admitted to the ICU, we can stratify the risk of in-hospital death for them by ePVS derived from Hakim formula, and ePVS derived from Hakim formula would be regarded as an indicator to evaluate the efficacy in the subsequent treatments during the hospitalization as well.

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Conflicts of Interest

None.

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