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ORIGINAL RESEARCH

Estimated Plasma Volume Status and the Risk of in-Hospital Mortality Among Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease in Intensive Care Unit: Retrospective Cohort Study from the eICU Collaborative Research Database

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Purpose: Globally, acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are the leading cause of hospitalization and mortality in COPD patients. The estimated plasma volume status (ePVS) is an indicator of fluid status that has been proven to correlate with the prognosis of intensive care unit (ICU) patients. Our study aims to explore the association of ePVS and in-hospital mortality in AECPD patients admitted in the ICU.

Methods: Data of this retrospective cohort study were extracted from the electronic Intensive Care Unit Collaborative Research Database (eICU-CRD). Outcome was the in-hospital mortality in AECOPD patients. The formulas, Duarte formula and Kaplan–Hakim (KH) formula, were used to assess ePVS. The weighted univariable and multivariable Cox regression models were utilized to explore the association of Duarte-ePVS and KH-ePVS and in-hospital mortality in AECOPD patients, with hazard ratios (HRs) and 95% confidence intervals (CIs). Kaplan-Meier survival analysis was used to pool the in-hospital mortality for different KH-ePVS levels. Restricted cubic splines curve analysis was used to assess the linear correlation of KH-ePVS and in-hospital mortality in AECOPD patients. These associations were further explored in different subgroups.

Results: In total, 2,773 AECOPD patients were included, of whom, 219 (7.90%) died within 6.24 (4.01–9.26) days. After adjusted confounding factors, we found AECOPD patients with high KH-ePVS level were associated with high risk of in-hospital mortality (HR=1.53, 95% CI: 1.05–2.24). No significant association was found between Duarte-ePVS and in-hospital mortality (P>0.05). The Kaplan-Meier analysis also suggested consistent association between KH-ePVS and in-hospital mortality in AECOPD patients. Subgroup analysis also suggested the association of KH-ePVS and in-hospital mortality in AECOPD patients remained robust.

Conclusion: Elevated KH-ePVS levels are associated with the high in-hospital mortality among AECOPD patients. As a simple and convenient indicator, KH-ePVS is expected to become a prognostic predictor for predicting in-hospital mortality in severe AECOPD patients.

Keywords: estimated plasma volume status, acute exacerbations of chronic obstructive pulmonary disease, in-hospital mortality, intensive care unit

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow obstruction and respiratory symptoms, affects approximately 400 million people and is expected to become the third leading cause of mortality and

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disability worldwide by 2030.[1,2] It is related to genetic, developmental, and social factors, and exposure to inhaled particulate matter (mainly cigarette smoke and air pollutants).[3] Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are episodes of symptoms of COPD that have significant adverse consequences for patients.[4] It is estimated that 22–40% of COPD patients suffer at least one moderate or severe exacerbation each year, while 9–16% of COPD patients suffer more than one. COPD patients with acute exacerbation experience accelerated lung function decline and increased risk of myocardial infarction, cerebrovascular events and death.[5] Therefore, it is essential to identify accurate predictors of prognosis in AECOPD patients.

During the hospitalization of AECOPD patients, fluid volume management is an extremely important treatment strategy. Fluid overload can lead to expiratory flow limitation (EFL), a dynamic state of maximal expiratory flow value, which results in a higher mortality risk in the ICU.[6,7] Clinically, plasma volume (PV) can evaluate the fluid balance of patients, and has been suggested to be related to the prognosis of critically ill patients in ICU by several epidemiological studies.[8–10] Traditionally, PV is measured by tracer dilution technology, but these methods are expensive, time consuming and complicated.[11] Hence, a noninvasive and easily available tool is necessary to assess the PV status. Estimated PV status (ePVS) is such a parameter based on hemoglobin and hematocrit, which is proposed to estimate the deviation of a patient's PV from the ideal PV.[12] Currently, there are two formulas to calculate ePVS, Duarte-ePVS and Kaplan–Hakim-ePVS (KH-ePVS), which have been proven to have different predictive abilities in predicting the outcome of ICU patients. He et al[13] suggested higher KH-ePVS is related to the poor prognosis of acute respiratory distress syndrome (ARDS), while observing no significant association between Duarte-ePVS and the outcome of ARDS patients. However, the associations of ePVS, calculated by Duarte and Kaplan–Hakim, and the risk of in-hospital mortality in AECOPD patients admitted to the ICU were not understood.

Herein, based on the electronic Intensive Care Unit Collaborative Research Database (eICU-CRD), we explored the association of ePVS and the in-hospital mortality in AECOPD patients admitted to the ICU. This study aims to find accurate markers for identifying poor prognosis of AECOPD and assist in the clinical management and risk stratification of AECOPD patients admitted to the ICU.

Methods

Data Source and Study Outcome

Data of this retrospective cohort study were extracted from eICU-CRD (version 2.0) (https://eicu-crd.mit.edu/), which was established by Philips Healthcare in collaboration with the Massachusetts Institute of Technology (MIT) Computational Physiology Laboratory. This database contains demographic, vital sign measurements, diagnostic information, and treatment information for more than 200,000 patients in 355 ICUs at 208 hospitals in the US during the period 2014–2015.[14] The present study used anonymous data available in the eICU database and was preapproved by the Institutional review board at the MIT.[15] The requirement of ethical approval for this was waived by the Institutional Review Board of Jian Yang Hospital of Traditional Chinese Medicine, because the data was accessed from eICU-CRD (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Jian Yang Hospital of Traditional Chinese Medicine due to the retrospective nature of the study.

The inclusion criteria were: (1) subjects aged ≥18 years old; (2) subjects diagnosed as AECOPD at the ICU admission; (3) subjects with examination of hematocrit, hemoglobin and weight upon ICU admission. The exclusion criteria were: (1) patients stayed in the ICU less than 24 h; (2) patients missing survival data.

Study Outcome

The study outcome of the present study was in-hospital mortality among AECOPD patients admitted to the ICU. Patient mortality information was accessed from the US Social Security Death Index.

The ePVS Calculation

The Duarte and Hakim formulas were utilized to calculate the ePVS in the present study. The Duarte formula included hematocrit and hemoglobin as follows: ePVS = [100-hematocrit (%)/hemoglobin (g/dL)].[16] The Hakim

formula[17] was derived by comparing actual volume (aPV) to ideal plasma volume (iPV). The aPV = (1-hematocrit) ×[a+(b× body weight)] (males: a = 1530; b = 41.0. females: a = 865; b = 47.9). The iPV = c× body weight (males: c = 39; females: c = 40). KH-ePVS = [(aPV-iPV)/iPV] × 100%. In the present study, Duarte-ePVS and KH-ePVS was divided into three levels. The low level of Duarte-ePVS was <96.81; medium Duarte-ePVS was 96.81–96.94; high Duarte-ePVS was ≥96.94. The low level of KH-ePVS was <−12.26; medium KH-ePVS was −12.26- −1.21; high level of KH-ePVS was ≥−1.21.

Potential Covariates

The potential covariates include demographic information [age (<65 and ≥65 years old), gender (male and female) and ethnicity (African American, Caucasian and other)], vital signs [heart rate, blood pressure, respiratory rate, temperature and oxyhemoglobin saturation (SPO_2)], vital signs [white blood cell (WBC), lymphocyte count, neutrophil count, platelet count, hematocrit, hemoglobin, red blood cell distribution width (RDW-CV), bilirubin, eGFR, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), albumin, blood urea nitrogen (BUN), glucose, calcium, anion gap and arterial blood gas test], interventions [vasopressors, mechanical ventilation, diuretic, erythropoietin and angiotensin converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ARB), complications (congestive heart failure, cardiogenic shock, sepsis, pneumonia, polycythemia, hematological system disease)] and scoring systems [Glasgow Coma Scale (GCS), age Above or Below 65 Years (CURB-65) and Acute Physiology, Age, Chronic Health Evaluation IV score (APACHE IV)]. If vital signs were collected multiple times or patients received more than one laboratory test during the hospitalization, the initial test data with the first 24 h after ICU admission were extracted for subsequent analysis.

Statistics Analysis

For the baseline characteristics, the normality of quantitative data was tested by skewness and kurtosis measurements, and the homogeneity of variance was tested by Levene's test. Normally distributed measurement data were described by [Mean (±SD)]. The *t*-test was used for comparison between groups with equal variance, and comparisons between groups with uneven variances were performed by t-test. Non-normal data were presented by the median and interquartile, and the Wilcoxon rank sum test was used for comparison between alive and dead groups. Count data was described as the number and percentage [n (%)], and Chi-square test or Fisher's exact test was used for comparison between alive and dead group. Multivariate imputation by chained equations (MICE) was used for missing data imputation. Sensitivity analysis was performed before and after missing data imputation (Supplementary Table 1).

The univariate and multivariate Cox regression models were utilized to explore the association of ePVS and KH-ePVS with in-hospital mortality among AECOPD patients admitted to the ICU, with hazard ratios (HRs) and 95% confidence intervals (CIs). Model 1 was a crude model without adjusting any covariates. Model 2 was adjusted gender, heart rate, ICU stay duration, sepsis, Apache score, CURB-65 and vasopressor. All statistical analyses were performed by SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided *P*-value <0.05 was considered statistically significant.

Results

Characteristics of AECOPD Patients

Figure 1 shows the flow chart for the screening of AECOPD patients. A total of 3,886 AECOPD patients aged ≥18 years old were screened from the EICU. Among them, 236 patients were missing hematocrit examination, 33 patients were missing hemoglobin examination, and 113 were missing weight examination upon ICU admission. 703 patients with the duration of ICU stay less than 24 h, and 28 patients missing survival data were excluded. Finally, 2,773 eligible AECOPD patients were included, with the mean age of 67.53 (±10.62). Of whom, 219 (7.90%) patients passed away and 2,554 patients survived within 6.24 (4.01–9.26) days. The proportion of patients with higher KH-ePVS levels was significantly higher in the dead group compared with survival group (49.77% vs 31.95%). No significant differences in ePVS levels were found between the alive and dead groups (*P*>0.05). The clinical and biochemical characteristics of the AECOPD patients are shown in Table 1.

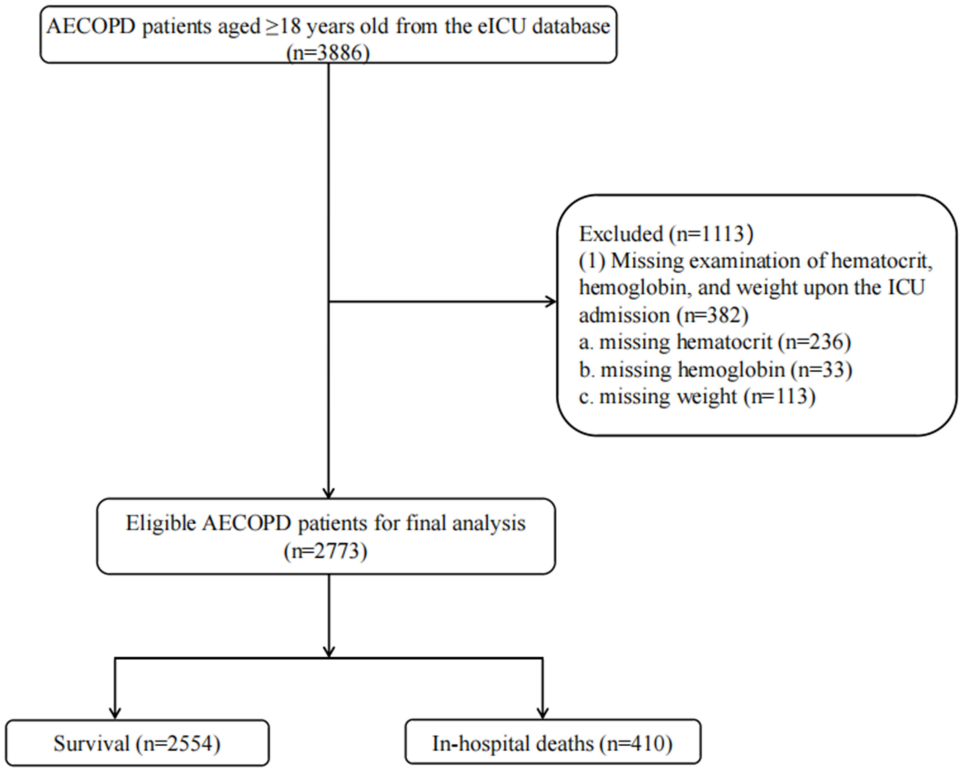

Figure 1 The flow chart of population screening.

Multivariable Cox Proportional Hazard Analysis of in-Hospital Mortality

As shown in Supplementary Table 2, it can be found that the risk of in-hospital mortality among AECOPD patients was related to gender, heart rate, ICU stay duration, sepsis, Apache score, CURB-65 and vasopressor (all $P<0.05$).

Table 1 Characteristics of AECOPD Patients

Variables	Total (N=2773)	Alive (N=2554)	Dead (N=219)	Statistics	*P*
Hospital Time, days, M (Q_1, Q_3)	6.24 (4.01–9.26)	6.24 (4.01–9.21)	6.32 (4.01–9.89)	W = 277,949	0.880
Duarte-ePVS, Mean (±SD)	96.87 (±0.17)	96.86 (±0.17)	96.87 (±0.18)	t = −0.425	0.671
KH-ePVS, Mean (±SD)	−6.24 (±13.49)	−6.73 (±13.42)	−0.49 (±12.99)	t = −6.619	<0.001
Duarte-ePVS, n (%)				χ^2 = 1.444	0.486
Low level	924 (33.32)	850 (33.28)	74 (33.79)		
Medium level	917 (33.07)	852 (33.36)	65 (29.68)		
High level	932 (33.61)	852 (33.36)	80 (36.53)		
KH-ePVS, n (%)				χ^2 = 37.419	<0.001
Low level	924 (33.32)	886 (34.69)	38 (17.35)		
Medium level	924 (33.32)	852 (33.36)	72 (32.88)		
High level	925 (33.36)	816 (31.95)	109 (49.77)		
Hematocrit, g/dL, Mean (±SD)	38.40 (±6.97)	38.58 (±6.95)	36.35 (±6.98)	t = 4.562	<0.001
Hemoglobin, g/dL, Mean (±SD)	12.29 (±2.33)	12.35 (±2.32)	11.65 (±2.32)	t = 4.261	<0.001
Weight, kg, Mean (±SD)	83.00 (±28.73)	83.81 (±28.86)	73.51 (±25.41)	t = 5.695	<0.001
Age, years, Mean (±SD)	67.53 (±10.62)	67.08 (±10.59)	72.74 (±9.62)	t = −8.275	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Total (N=2773)	Alive (N=2554)	Dead (N=219)	Statistics	*P*
Age, years, n (%)				χ^2 = 33.741	<0.001
<65	1086 (39.16)	1041 (40.76)	45 (20.55)		
≥65	1687 (60.84)	1513 (59.24)	174 (79.45)		
Gender, n (%)				χ^2 = 0.747	0.388
Female	1499 (54.06)	1374 (53.8)	125 (57.08)		
Male	1274 (45.94)	1180 (46.2)	94 (42.92)		
Ethnicity, n (%)				χ^2 = 11.078	0.004
African American	244 (8.8)	234 (9.16)	10 (4.57)		
Caucasian	2309 (83.27)	2109 (82.58)	200 (91.32)		
Other	220 (7.93)	211 (8.26)	9 (4.11)		
Height, cm, Mean (±SD)	167.62 (±10.26)	167.71 (±10.30)	166.60 (±9.80)	t = 1.537	0.124
BMI, kg/m^2, Mean (±SD)	29.51 (±9.93)	29.77 (±9.98)	26.46 (±8.82)	t = 5.270	<0.001
BMI, kg/m^2, n (%)				χ^2 = 14.746	0.001
<25	1046 (37.72)	943 (36.92)	103 (47.03)		
25–30	637 (22.97)	581 (22.75)	56 (25.57)		
≥30	1090 (39.31)	1030 (40.33)	60 (27.4)		
SBP, mmHg, Mean (±SD)	130.62 (±27.79)	131.23 (±27.39)	123.45 (±31.28)	t = 3.566	<0.001
DBP, mmHg, Mean (±SD)	73.40 (±18.56)	73.74 (±18.47)	69.44 (±19.18)	t = 3.295	0.001
MAP, mmHg, Mean (±SD)	92.47 (±19.68)	92.90 (±19.45)	87.44 (±21.64)	t = 3.611	<0.001
Heart Rate, bpm, Mean (±SD)	97.67 (±20.37)	97.34 (±20.18)	101.58 (±22.15)	t = −2.738	0.007
Respiratory Rate, insp/min, Mean (±SD)	22.96 (±6.72)	22.90 (±6.69)	23.66 (±7.09)	t = −1.609	0.108
Temperature, Deg.C, Mean (±SD)	36.80 (±0.73)	36.81 (±0.71)	36.66 (±0.86)	t = 2.459	0.015
ICU Stay Duration, min, M (Q_1, Q_3)	3909 (2454–6770)	3756 (2424.5–6413.5)	6026 (3597.5–10386)	W = 193,011.5	<0.001
Sepsis, n (%)				χ^2 = 57.569	<0.001
No	2406 (86.77)	2253 (88.21)	153 (69.86)		
Yes	367 (13.23)	301 (11.79)	66 (30.14)		
Pneumonia, n (%)				χ^2 = 8.543	0.003
No	1932 (69.67)	1799 (70.44)	133 (60.73)		
Yes	841 (30.33)	755 (29.56)	86 (39.27)		
Cardiogenic Shock, n (%)				-	0.077
No	2760 (99.53)	2544 (99.61)	216 (98.63)		
Yes	13 (0.47)	10 (0.39)	3 (1.37)		
Congestive Heart Failure, n (%)				χ^2 = 1.847	0.174
No	2171 (78.29)	2008 (78.62)	163 (74.43)		
Yes	602 (21.71)	546 (21.38)	56 (25.57)		
Hematological System Diseases, n (%)				χ^2 = 14.570	<0.001
No	2502 (90.23)	2321 (90.88)	181 (82.65)		
Yes	271 (9.77)	233 (9.12)	38 (17.35)		
Polycythemia, n (%)				χ^2 = 6.322	0.012
No	2574 (92.82)	2361 (92.44)	213 (97.26)		
Yes	199 (7.18)	193 (7.56)	6 (2.74)		
Apache Score, Mean (±SD)	56.80 (±20.66)	55.14 (±19.29)	76.23 (±25.73)	t = −11.846	<0.001
CURB-65, Mean (±SD)	2.36 (±1.02)	2.31 (±1.00)	3.04 (±1.02)	t = −10.388	<0.001
Vasopressor, n (%)				χ^2 = 161.162	<0.001
No	2578 (92.97)	2421 (94.79)	157 (71.69)		
Yes	195 (7.03)	133 (5.21)	62 (28.31)		
Erythropoietin, n (%)				-	1.000
No	2771 (99.93)	2552 (99.92)	219 (100)		
Yes	2 (0.07)	2 (0.08)	0 (0)		

(*Continued*)

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Table 1 (Continued).

Variables	Total (N=2773)	Alive (N=2554)	Dead (N=219)	Statistics	*P*
Diuretic, n (%)				χ^2 = 2.568	0.109
No	2374 (85.61)	2195 (85.94)	179 (81.74)		
Yes	399 (14.39)	359 (14.06)	40 (18.26)		
ACEI/ARB, n (%)				χ^2 = 0.000	1.000
No	2667 (96.18)	2456 (96.16)	211 (96.35)		
Yes	106 (3.82)	98 (3.84)	8 (3.65)		
Mechanical Ventilation, n (%)				χ^2 = 31.217	<0.001
No	1870 (67.44)	1760 (68.91)	110 (50.23)		
Yes	903 (32.56)	794 (31.09)	109 (49.77)		
WBC, K/mcL, M (Q_1, Q_3)	11 (8.1–14.9)	10.9 (8.04–14.6)	13.4 (8.91–18.58)	W = 225,822	<0.001
Platelets, K/mcL, Mean (±SD)	233.60 (±94.47)	233.54 (±93.70)	234.41 (±103.19)	t = −0.121	0.904
RDW, %, Mean (±SD)	15.47 (±2.23)	15.47 (±2.21)	15.56 (±2.38)	t = −0.625	0.532
Creatinine, mg/dL, M (Q_1, Q_3)	0.96 (0.7–1.4)	0.94 (0.7–1.37)	1.1 (0.76–1.73)	W = 247,808	0.005
eGFR, mL/min/1.73m^2, Mean (±SD)	74.61 (±29.84)	75.33 (±29.68)	66.23 (±30.53)	t = 4.341	<0.001
BUN, mg/dL, Mean (±SD)	25.90 (±18.42)	25.24 (±17.89)	33.59 (±22.37)	t = −5.376	<0.001
Glucose, mg/dL, Mean (±SD)	163.29 (±72.36)	162.81 (±72.56)	168.89 (±69.93)	t = −1.192	0.233
Calcium, mg/dL, M (Q_1, Q_3)	8.9 (8.4–9.3)	8.9 (8.5–9.3)	8.7 (8.2–9.2)	W = 315,493.5	0.002
Anion Gap, Mean (±SD)	12.91 (±4.56)	12.88 (±4.52)	13.34 (±5.00)	t = −1.340	0.181
SPO2, mmHg, M (Q_1, Q_3)	96 (93–98)	96 (93–98)	95.6 (91.7–99)	W = 288,212.5	0.451

Abbreviations: SD: standard deviation; M: median; Q_1: 1st quartile; Q_3: 3rd quartile; t: student's *t*-test; t : Satterthwaite *t*-test; W: Wilcoxon rank sum test; χ^2: chi-square test; ePVS: estimated plasma volume status; KH-ePVS: Kaplan-Hakim estimated plasma volume status; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; ICU: intensive care unit; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; WBC: white blood cell; RDW: red blood cell distribution width; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; SPO2: oxyhemoglobin saturation.

KH-ePVS, ePVS and in-Hospital Mortality Among AECOPD Patients

Two Cox proportional hazard models were utilized to explore the association of KH-ePVS and ePVS with in-hospital mortality among AECOPD patients admitted to the ICU, as depicted in Table 2 and Figure 2. After adjusted gender, heart rate, ICU stay duration, sepsis, Apache score, CURB-65 and vasopressor, patients with high KH-ePVS level had a 53%

Table 2 KH-ePVS, Duarte-ePVS and in-Hospital Mortality of AECOPD Patients

Variables	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Duarte-ePVS	1.03 (0.90–1.19)	0.633	1.08 (0.94–1.24)	0.277
KH-ePVS	1.37 (1.21–1.55)	<0.001	1.15 (1.01–1.32)	0.041
Duarte-ePVS				
Low level	Ref		Ref	
Medium level	0.91 (0.65–1.27)	0.579	0.99 (0.71–1.38)	0.948
High level	1.14 (0.83–1.57)	0.409	1.29 (0.93–1.78)	0.127
KH-ePVS				
Low level	Ref		Ref	
Medium level	1.77 (1.20–2.62)	0.004	1.44 (0.97–2.15)	0.072
High level	2.30 (1.59–3.33)	<0.001	1.53 (1.05–2.24)	0.029

Notes: Model 1: crude model; Model 2: adjusted gender, heart rate, ICU stay duration, sepsis, Apache score, CURB-65 and vasopressor.

Abbreviations: HR, hazard ratio; CI, confidence intervals; Ref, reference; AECOPD, acute exacerbations of chronic obstructive pulmonary disease.

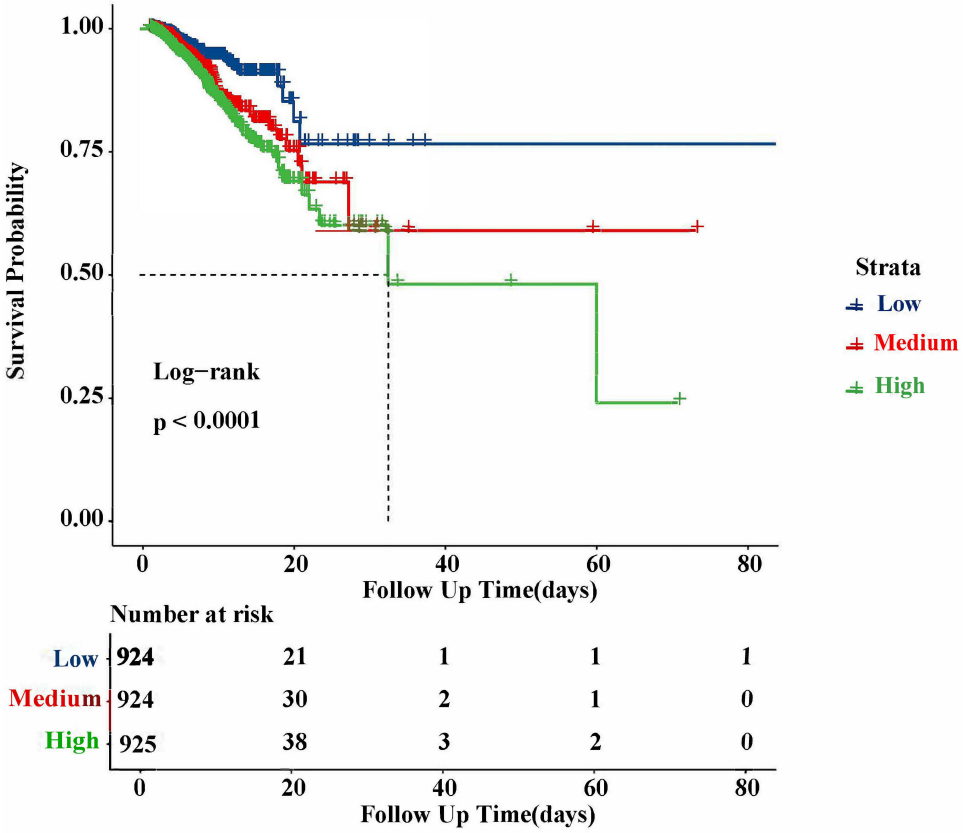

Figure 2 The Kaplan Meier curve of KH-ePVS and in-hospital mortality among AECOPD patients.

increased risk of in-hospital mortality compared with those with low KH-ePVS level (HR = 1.53, 95% CI: 1.05–2.24); while, no statistically significant associations were observed between Duarte-ePVS and in-hospital mortality (P>0.05).

Association of KH-ePVS with in-Hospital Mortality Based on Different Age, Gender and Complications

Subgroup analysis were performed to further explore the association of KH-ePVS with in-hospital mortality among AECOPD patients based on age, gender, the history of sepsis and congestive heart failure. The results are shown in Figure 3. After all covariates were adjusted, we found the association of KH-ePVS and in-hospital mortality was still robust, especially among AECOPD patients without a history of sepsis (HR = 1.78, 95% CI: 1.11–2.85) and congestive heart failure (HR = 2.19, 95% CI: 1.34–3.56).

Discussion

Based on the eICU-CRD database, we explored the association between ePVS assessed by two different methods, Duarte-ePVS and KH-ePVS, and the risk of in-hospital all-cause mortality in AECOPD patients. Our findings suggested that high KH-ePVS was related to high in-hospital mortality risk in AECOPD patients, while no significant statistical association of Duarte-ePVS and in-hospital mortality was found. There was potential benefit in monitoring KH-ePVS levels to assist in the clinical management and prediction of prognosis of AECOPD patients in the ICU.

In patients admitted to the ICU, fluid management is essential in order to restore cardiac output, systemic blood pressure, and renal perfusion. Clinically, patients with COPD were often accompanied by EFL, resulting in a higher risk of death. Direct quantification of PV, representing the status of fluid balance, has been proven to have clinical utility to reveal volume overload in several diseases, however, this methodology has not been readily available to clinicians due to its being costly, time consuming and complex.[11] Some hemodialysis equipment used hematocrit to monitor volume during hemodialysis, but this

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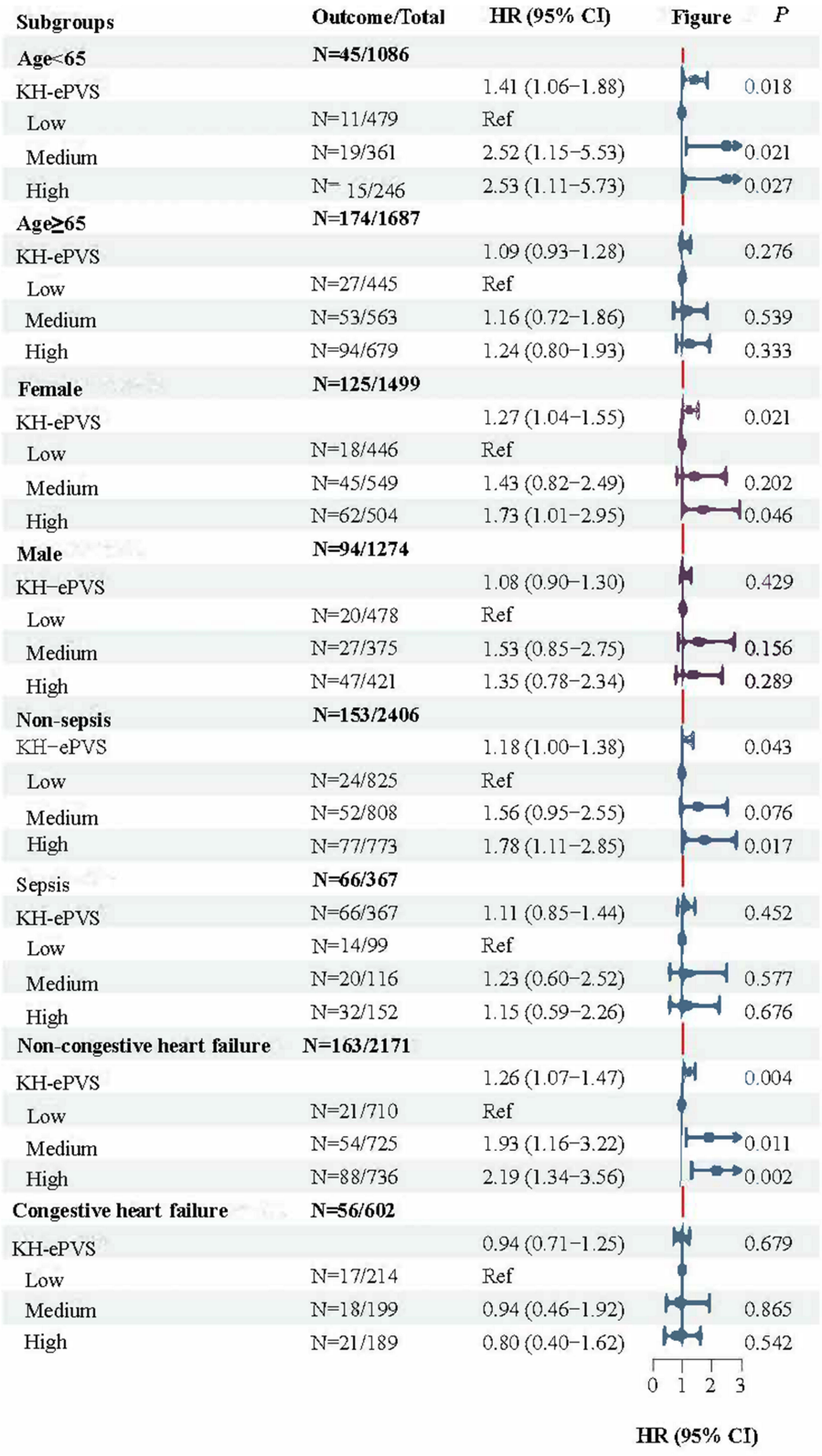

Figure 3 Subgroup analysis of KH-ePVS and in-hospital mortality among AECOPD patients.

methodology is less precise in assessing PV status.[18] Previous studies reported that the ePVS, calculated from blood count and/or body weight has been associated with the poor outcome of pulmonary disease.[10,12] Duarte-ePVS was first derived by Duarte et al[16] and the prognostic value of Duarte-ePVS in severe respiratory disease was suggested.[10,12] A retrospective, multicenter observational study reported that a lower ePVS on admission related to a greater chance of survival in COVID-19-related ARDS patients,[12] however, there was no significant association found between KH-ePVS and outcome of ARDS patients, which was inconsistent with our results. Previous studies reported the similar accuracy of Duarte-ePVS and KH-ePVS for predicting in-hospital death in ICU patients.[19,20] However, our study found high KH-ePVS, but not Duarte-ePVS, was associated with poor outcome in AECOPD patients admitted to the ICU. KH-ePVS may be a more powerful predictor of AECOPD patients admitted to the ICU.

Over-activation of the renin-angiotensin-aldosterone system may be associated with high plasma load and increased mortality risk in patients with AECOPD.[21] The angiotensin-converting enzyme (ACE) is abundant in the lung. When AECOPD occurred, ACE was activated by acute alveolar hypoxia, increasing the production of angiotensin II (Ang II), an important mediator of lung injury and apoptosis.[22] It can mediate inflammatory response by interfering with cytokine production, inflammatory cell migration, epithelial apoptosis, oxidative stress, activation of tissue mast cells and lung fibrosis.[23,24] Ang II also can induce bronchoconstriction, leading to the deterioration of lung function.[25] Basic experiments in the next step are need to further explore the association of renin-angiotensin-aldosterone system and high plasma load in patients with AECOPD.

To the best of our knowledge, this was the first retrospective cohort study to explore the association of Duarte-ePVS, KH-ePVS and in-hospital mortality in AECOPD patients admitted to the ICU. KH-ePVS is calculated by the KH formula established by Kaplan-Hakim et al based on hematocrit, bodyweight and gender. Our results observed that high KH-ePVS remained significantly connected to in-hospital mortality after multivariate adjustment. Our study has certain clinical significance. Clinicians can relatively objectively judge the PV status of patients with AECOPD by calculating KH-ePVS and formulate standardized personalized treatment plans. In clinical practice, compared with methods such as measuring PV using radioisotope analysis and evaluating the patient's congestion status by echocardiography, KH-ePVS has the advantages of low-cost, strong practicality, and is not affected by the level of equipment and operators. It is expected to become a useful indicator for the short-term prognosis of AECOPD patients in the ICU. However, several limitations should be recognized in the present study. First, only US data were included for exploring the association of ePVS and the prognosis of AECOPD patients, which could potentially limit the generalizability of the association extrapolated to other races. Second, we did not directly measure PV by radioisotope assays, although these techniques were relatively impractical and expensive in routine clinical practice. The consistency with estimated and measured PV remains controversial.[11] Third, due to the nature of the single-center retrospective study, limited sample size and data bias were inevitable despite strong statistical corrections. However, the inclusion criteria were performed strictly so that the cases included reflected the actual conditions as accurately as possible. Additionally, the present study could provide only the relationship between KH-ePVS and in-hospital mortality in AECOPD patients admitted to the ICU rather than causality. Future research should aim to expand sample sources to include a wider range of regions and patient types to improve the generalizability of the findings.

Conclusion

Our study suggested that high KH-ePVS is associated with high in-hospital mortality among ICU patients with AECOPD. Moreover, KH-ePVS appears to have a more accurate predictive value than Duarte-ePVS in predicting the prognosis of AECOPD patients admitted to the ICU. However, the role of ePVS in guiding fluid management should be investigated in a future large-scale prospective cohort study.

Ethics Approval and Informed Consent

The requirement of ethical approval for this was waived by the Institutional Review Board of Jian Yang Hospital of Traditional Chinese Medicine, because the data were accessed from eICU-CRD (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Jian Yang Hospital of Traditional Chinese Medicine due to the retrospective nature of the study.

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Disclosure

The authors report no conflicts of interest in this work.

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