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ORIGINAL ARTICLE

Early estimated pulse wave velocity as a prognostic marker in critically ill patients with hemorrhagic stroke: A retrospective analysis of the MIMIC-IV database

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Abstract

BACKGROUND: The estimated pulse wave velocity (ePWV) calculated using chronological age and blood pressure has been used as a valuable measure of vascular aging. This study aimed to investigate the relationship between early ePWV and all-cause mortality in critically ill patients with hemorrhagic stroke.
METHODS: This study included hemorrhagic stroke patients from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Participants were categorized into four quartiles based on the ePWV values. The primary outcome was 30-day mortality, and the secondary outcomes were 90-day and 1-year mortality. Cox proportional risk models and restricted cubic spline analyses were conducted to assess the hazard ratio (HR) and 95% confidence interval (CI) for the association between ePWV and outcomes. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of ePWV.
RESULTS: For 30-day mortality, after adjusting for all confounders, the association remained significant with ePWV considered as a continuous variable (HR, 95% CI: 1.21 [1.16, 1.26]; $p < 0.001$). The HR with 95% CI for the second, third, and fourth quartile groups were 1.40 (1.07, 1.83), 1.82 (1.37, 2.42), and 3.15 (2.30, 4.32), respectively, compared to the first quartile group. Also, ePWV was found to have a linear relationship with 30-day mortality. Similar findings were found for 90-day mortality and 1-year mortality. When ePWV was incorporated into conventional disease severity scoring systems, the predictive performance of these systems was significantly improved.

CONCLUSIONS: This study revealed that higher levels of early ePWV are significantly associated with increased all-cause mortality in critically ill patients with hemorrhagic stroke. ePWV may be a promising prognostic marker for critically ill patients with hemorrhagic stroke.

Abbreviations:

ICH	- intracerebral hemorrhage
SAH	- subarachnoid hemorrhage
ICU	- intensive care unit
PWV	- pulse wave velocity
ePWV	- estimated pulse wave velocity
MAP	- mean arterial pressure
MIMIC-IV	- Medical Information Mart for Intensive Care IV
BIDMC	- Beth Israel Deaconess Medical Center
MIT	- Massachusetts Institute of Technology
IRB	- Institutional Review Board
ICD	- International Classification of Diseases
SBP	- systolic blood pressure
DBP	- diastolic blood pressure
CPD	- chronic pulmonary disease
SOFA	- sequential organ failure assessment
APS III	- acute physiology score III
GCS	- Glasgow coma scale
CCI	- Charlson comorbidity index
RDW	- red cell distribution width
WBC	- white blood cell
BUN	- blood urea nitrogen
INR	- international normalized ratio
PT	- prothrombin time
PTT	- partial thromboplastin time
MV	- mechanical ventilation
RRT	- renal replacement treatment
SD	- standard deviation
IQR	- interquartile range
ROC	- receiver operating characteristic
AUROC	- area under the receiver operating characteristic curve
HR	- hazard ratio
CI	- confidence interval

INTRODUCTION

Stroke impacts up to one in five individuals throughout their lifetime in some high-income countries and nearly one in two in low-income countries. On a global scale, it ranks as the second leading cause of mortality (Hilkens *et al.* 2024). Hemorrhagic strokes, including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), account for about 20% of all strokes and are the second most common type of stroke. Hemorrhagic stroke results from the rupture of a blood vessel, leading to bleeding into the brain. This highly morbid condition often results in mortality or neurological impairment among survivors (McKinney *et al.* 2015). Moreover, the rates of mortality and disability associated with hemorrhagic stroke are significantly higher than those associated with ischemic stroke (Zhang *et al.* 2024). Even in high-income countries, neither early nor long-term case-fatality rates due to hemorrhagic stroke have consistently shown improvement over the past decades (Hsieh *et al.* 2021). With the aging of the global population, the burden of hemorrhagic stroke, particularly in intensive care units (ICUs), is increasing. Therefore, early risk stratification and comprehensive treatment of hemorrhagic stroke are of paramount importance (Huang *et al.* 2024).

Measurement of pulse wave velocity (PWV) is the most commonly used noninvasive method for assessing arterial stiffness (Quinn *et al.* 2012). As an emerging biomarker, PWV has been widely used in cardiovascular risk stratification, blood pressure assessment, and cardiovascular drug efficacy evaluation (Pereira *et al.* 2015). Additionally, some studies focused on the relationship between PWV and the onset or prognosis of cerebrovascular diseases. Several studies have shown a significant association between elevated PWV and the development of cerebral small vessel disease (Kim *et al.* 2016; Munakata, 2020). Also, an elevated PWV level increases the risk of short-term poor outcomes among patients with cerebral ischemic stroke (Kim *et al.* 2014). However, there are limited studies on the association between PWV and mortality in hemorrhagic stroke patients.

It is worth noting that while PWV serves as a marker for assessing arterial stiffness, its clinical application is limited due to the requirement of specialized equipment for detection. Recently, the estimated pulse wave velocity (ePWV) calculated using chronological age and mean arterial pressure (MAP) has been validated and used as a valuable measure of vascular aging (Heffernan *et al.* 2023). Previous studies have shown that ePWV is associated with outcomes in various diseases, including diabetes, heart failure, acute kidney injury, and coronary artery disease (Chen *et al.* 2023; Cui *et al.* 2024; Wu *et al.* 2023; Yuan *et al.* 2024). ePWV was also recognized as an independent risk factor for long-term mortality in the stroke population (Huang *et al.* 2023). However, to date, there are few studies on the relationship between ePWV and risk of short-term mortality in hemorrhagic stroke patients. Based on the above-mentioned knowledge gap, we performed a cohort study utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to explore the association of early ePWV with all-cause mortality in critically ill patients with hemorrhagic stroke.

MATERIALS AND METHODS

Data Source

The data for this retrospective cohort study was obtained from the MIMIC-IV database (version 3.0), encompassing comprehensive information on 94,458 hospital stays in ICU at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2022. The information has been anonymized and approved by the Massachusetts Institute of Technology (MIT) and the BIDMC Institutional Review Boards (IRBs) for conducting scientific research. The corresponding author (Duo Yang) complied with the requirements for accessing the database and was responsible for

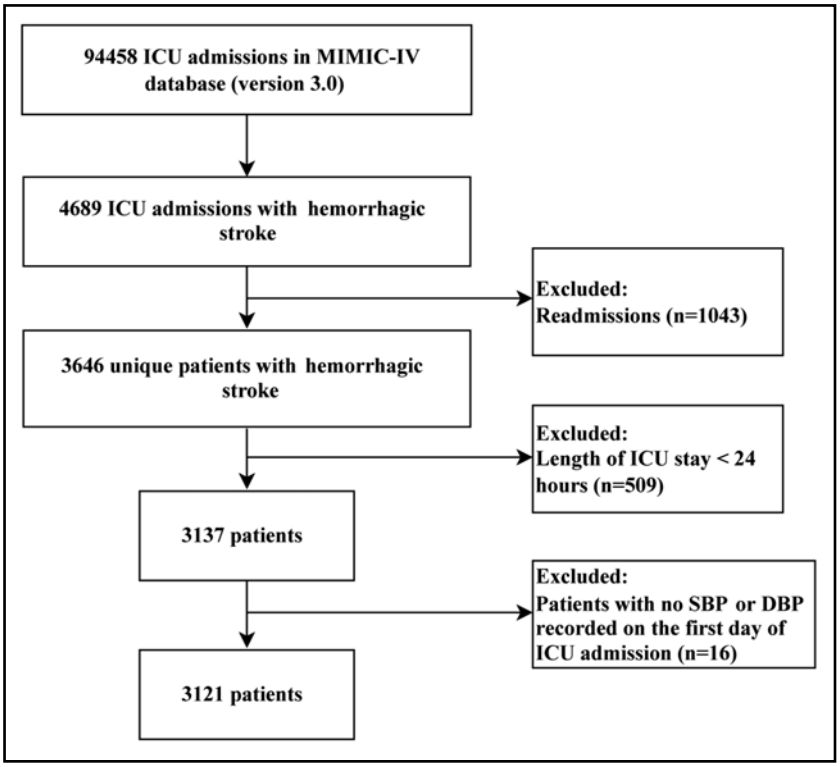

Fig. 1. Flowchart of the study cohort. Abbreviations: ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV; SBP, systolic blood pressure; DBP, diastolic blood pressure.

data extraction (certification number: 48247201). The present study adhered to the principles outlined in the Declaration of Helsinki and followed the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology.

Study participants

This study included adult critically ill patients (age > 18 years) who were diagnosed with hemorrhagic stroke using the ninth or tenth version of the International Classification of Diseases (ICD). The patients were identified using ICD-9 codes 430 and 431 and ICD-10 codes I60x and I61x (Hsieh *et al.* 2021; Yang *et al.* 2023). Patients were excluded when data for systolic blood pressure (SBP) or diastolic blood pressure (DBP) on the first day admitted to the ICU were missing. In addition, patients with an ICU stay duration of less than 24 hours were also excluded. Finally, only the data from the initial ICU stay were analyzed for patients who had multiple ICU admissions.

Data extraction

Navicat Premium software (version 12.0.11) and Structured Query Language were utilized to acquire the following patients' information: (1) demographics: age, sex, and race; (2) comorbidities: hypertension, atrial fibrillation, myocardial infarct, chronic pulmonary disease (CPD), diabetes, renal disease, liver disease, and malignant tumor; (3) disease severity scores: sequential organ failure assessment (SOFA), acute physiology score III (APS III), Glasgow coma scale (GCS), and Charlson comorbidity index (CCI); (4) vital signs and laboratory parameter data on the first day of ICU admission: heart rate (HR), SBP, DBP, respiratory rate (RR), saturation of pulse oximetry (SpO_2), temperature, hemoglobin, red cell distribution width (RDW), white blood cell (WBC), platelet, anion gap, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, international normalized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT); (5) treatments: mechanical ventilation (MV), renal replacement treatment (RRT), use of vasopressors, and neurosurgery.

The exposure variable of this study, ePWV, was determined using the following formula: $ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MAP + 3.176 \times 10^{-3} \times age \times MAP - 1.832 \times 10^{-2} \times MAP$. MAP was calculated as (DBP) + 0.4 × (SBP - DBP) (Aimagambetova *et al.* 2024). Considering the multiple blood pressure measurements taken within the first 24 h of ICU admission, we derived ePWV values from each SBP and DBP measurement and subsequently calculated the mean ePWV values to represent patients' level of arterial stiffness. The vital signs and laboratory parameter data on the first day of ICU admission were also averaged and utilized for subsequent statistical analysis. The primary outcome was all-cause 30-day mortality, with secondary outcomes being all-cause 90-day mortality and 1-year mortality following ICU admission.

Statistical analysis

The cutoff value of ePWV in our study was not specified due to the variations in ePWV cutoff values reported in other studies. Instead, the ePWV values were divided

Tab. 1. Baseline characteristics of the study population according to ePWV quartiles

Characteristics	Total	ePWV				*p*-Value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
		< 8.45	≥ 8.45, < 10.33	≥ 10.33, < 12.66	≥ 12.66	
Included patients	3121	779	780	780	782	
Age (years)	66.2 ± 15.9	46.0 ± 10.0	61.2 ± 6.1	72.6 ± 5.3	84.8 ± 4.6	< 0.001
Sex (male)	1597 (51.2)	387 (49.7)	426 (54.6)	419 (53.7)	365 (46.7)	0.005
Race (White)	1815 (58.2)	405 (52.0)	439 (56.3)	449 (57.6)	522 (66.8)	< 0.001
Comorbidities						
Hypertension	1827 (58.5)	326 (41.8)	475 (60.9)	528 (67.7)	498 (63.7)	< 0.001
Atrial fibrillation	710 (22.7)	31 (4.0)	109 (14.0)	208 (26.7)	362 (46.3)	< 0.001
Myocardial infarct	262 (8.4)	32 (4.1)	68 (8.7)	76 (9.7)	86 (11.0)	< 0.001
CPD	394 (12.6)	79 (10.1)	93 (11.9)	123 (15.8)	99 (12.7)	0.008
Diabetes	685 (21.9)	96 (12.3)	169 (21.7)	227 (29.1)	193 (24.7)	< 0.001
Renal disease	321 (10.3)	30 (3.9)	64 (8.2)	98 (12.6)	129 (16.5)	< 0.001
Liver Disease	160 (5.1)	68 (8.7)	52 (6.7)	29 (3.7)	11 (1.4)	< 0.001
Malignant tumor	258 (8.3)	55 (7.1)	70 (9.0)	74 (9.5)	59 (7.5)	0.253
Disease severity scores						
SOFA	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.5 (1.0, 4.0)	3.0 (1.8, 4.0)	3.0 (2.0, 5.0)	< 0.001
APS III	37.6 ± 17.8	36.6 ± 20.5	37.3 ± 18.8	37.6 ± 16.1	39.0 ± 15.1	0.062
GCS	12.7 ± 3.1	13.2 ± 3.1	12.8 ± 3.2	12.6 ± 3.1	12.1 ± 3.1	< 0.001
CCI	5.0 (3.0, 7.0)	2.0 (1.0, 4.0)	4.0 (3.0, 6.0)	6.0 (4.0, 7.0)	7.0 (6.0, 8.8)	< 0.001
Vital signs						
HR (bpm)	79.6 ± 13.6	80.5 ± 14.3	79.9 ± 14.0	79.1 ± 13.0	79.1 ± 13.2	0.136
MAP (mmHg)	91.9 ± 10.1	88.0 ± 8.4	92.6 ± 10.0	93.2 ± 10.5	93.8 ± 10.3	< 0.001
RR (bpm)	18.6 ± 3.2	18.5 ± 3.7	18.3 ± 3.3	18.6 ± 3.0	18.9 ± 2.8	< 0.001
SpO_2 (%)	97.1 ± 1.9	97.5 ± 1.8	97.0 ± 2.1	97.0 ± 1.9	96.9 ± 1.9	< 0.001
Temperature (°C)	37.0 ± 0.5	37.0 ± 0.5	37.0 ± 0.5	37.0 ± 0.4	36.9 ± 0.5	< 0.001

into quartiles. Participant characteristics were analyzed according to the ePWV quartiles. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and were compared using one-way ANOVA or Kruskal–Wallis test. Categorical variables were presented as frequencies and percentages, and the chi-square test was used for comparison.

The Kaplan–Meier curves were used to visualize survival analysis results, which were compared using the log-rank tests. The associations between ePWV and outcomes were assessed using univariable and multivariable Cox proportional hazard models. ePWV was considered both as a categorical variable (divided into quartiles) and as a continuous variable. For multivariable Cox proportional hazard models, covariates were selected based on biological plausibility, previous findings, and statistical significance in the univariable Cox regression models. The results of univariable Cox regression analyses of covariates and 30-day mortality are shown in Table S1. Additionally, we employed a Cox regression model to incorporate covariates into the basic model or gradually eliminate them in the complete model, subsequently comparing the regression coefficients. Covariates that caused more than a 10% change in initial regression coefficients were included (Jaddoe *et al.* 2014). If the variance inflation factor was greater than 4, collinearity was considered to exist, and the covariate was removed from the model. For the minimally-adjusted model (Model 2), we adjusted for sex and race. For the fully-adjusted model (Model 3), we further adjusted for hypertension, atrial fibrillation, myocardial infarct, CPD, diabetes, renal disease, liver disease, malignant tumor, SOFA, APS III, GCS, CCI, HR, RR, SpO_2, temperature, hemoglobin, RDW, WBC, platelet, anion gap, bicarbonate, BUN, creatinine, glucose, INR, PT, PTT, MV, RRT, vasopressors, and neurosurgery.

Restricted cubic spline analyses were performed to assess linear relationship between ePWV and

Characteristics	Total	ePWV				*p*-Value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
		< 8.45	≥ 8.45, < 10.33	≥ 10.33, < 12.66	≥ 12.66	
Laboratory parameters						
Hemoglobin (g/dL)	12.4 ± 1.9	12.4 ± 2.0	12.6 ± 2.1	12.4 ± 1.9	12.1 ± 1.8	< 0.001
RDW (%)	14.0 ± 1.6	13.8 ± 1.7	13.9 ± 1.6	14.1 ± 1.6	14.1 ± 1.5	< 0.001
WBC ($\times 10^9$/L)	11.6 ± 8.0	12.6 ± 5.5	12.0 ± 10.6	11.4 ± 6.5	10.4 ± 8.4	< 0.001
Platelet ($\times 10^9$/L)	218.8 ± 81.3	229.6 ± 85.2	222.1 ± 84.1	217.0 ± 81.4	206.4 ± 72.5	< 0.001
Anion gap (mmol/L)	14.4 ± 3.0	14.5 ± 3.3	14.5 ± 3.0	14.5 ± 2.8	14.2 ± 3.0	0.239
Bicarbonate (mmol/L)	23.0 ± 3.1	22.4 ± 3.3	23.1 ± 3.2	23.1 ± 3.0	23.5 ± 3.0	< 0.001
BUN (mg/dL)	15.3 (11.8, 21.0)	12.2 (9.7, 16.7)	14.8 (11.5, 19.1)	16.5 (13.0, 23.0)	18.0 (14.0, 23.0)	< 0.001
Creatinine (mg/dL)	0.8 (0.7, 1.1)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)	0.9 (0.8, 1.1)	< 0.001
Glucose (mg/dL)	143.1 ± 50.1	139.9 ± 46.3	149.2 ± 57.7	145.7 ± 50.1	137.8 ± 44.6	< 0.001
INR	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	0.002
PT (s)	13.3 ± 4.3	13.5 ± 6.5	12.9 ± 3.3	13.1 ± 3.0	13.6 ± 3.4	0.010
PTT (s)	30.2 ± 10.1	31.0 ± 11.5	30.3 ± 9.3	29.5 ± 9.3	30.0 ± 10.2	0.052
Treatments						
MV	1293 (41.4)	375 (48.1)	359 (46.0)	325 (41.7)	234 (29.9)	< 0.001
RRT	81 (2.6)	38 (4.9)	21 (2.7)	15 (1.9)	7 (0.9)	< 0.001
Vasopressors	580 (18.6)	197 (25.3)	173 (22.2)	122 (15.6)	88 (11.3)	< 0.001
Neurosurgery	1028 (32.9)	339 (43.5)	287 (36.8)	244 (31.3)	158 (20.2)	< 0.001
Outcomes						
30-day mortality	718 (23.0)	112 (14.4)	152 (19.5)	183 (23.5)	271 (34.7)	< 0.001
90-day mortality	860 (27.6)	137 (17.6)	171 (21.9)	227 (29.1)	325 (41.6)	< 0.001
1-year mortality	1063 (34.1)	155 (19.9)	218 (27.9)	291 (37.3)	399 (51.0)	< 0.001

Note: Variables are presented as mean ± SD, N (%), or median (IQR).
Abbreviations: ePWV, estimated pulse wave velocity; CPD, chronic pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; GCS, Glasgow coma scale; CCI, Charlson comorbidity index; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SpO2, saturation of pulse oximetry; RDW, red cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; MV, mechanical ventilation; RRT, renal replacement therapy; SD, standard deviation; IQR, interquartile range.

all-cause mortality. To identify effect modifications, subgroup analyses were performed by sex, race, comorbidities, and treatments. Likelihood ratio tests were performed to assess interactions between subgroups. To further evaluate the performance of ePWV, SOFA, APS III, and their combinations in predicting 30-day mortality, receiver operating characteristic (ROC) curve analyses were conducted. Additionally, DeLong tests were employed to compare the area under the receiver operating characteristic curves (AUROCs) of ePWV, SOFA, APS III, and their combinations. No more than 5% of each variable in this study was missing. Multiple imputation was conducted to address missing values. As a sensitivity analysis, we reanalyzed whether the relationship between ePWV and outcomes would change in the complete case dataset.

Data analyses were performed using the statistical software package R, version 4.3.0 (R Foundation, Vienna, Austria) and Free Statistics software, version 1.9.2. Differences with a two-sided $p < 0.05$ were considered to be statistically significant.

RESULTS

Patient selection

Of the 94,458 ICU stays, 4,689 critically ill patients with hemorrhagic stroke were identified. The flowchart of this study is shown in Fig. 1. The cohort for the final data analyses included 3,121 participants.

Baseline characteristics

The baseline characteristics of all participants are shown in Table 1. The patients included in the study were categorized into quartiles based on their ePWV levels as follows: Quartile 1, < 8.45; Quartile 2, ≥ 8.45 and < 10.33; Quartile 3, ≥ 10.33 and < 12.66; Quartile 4,

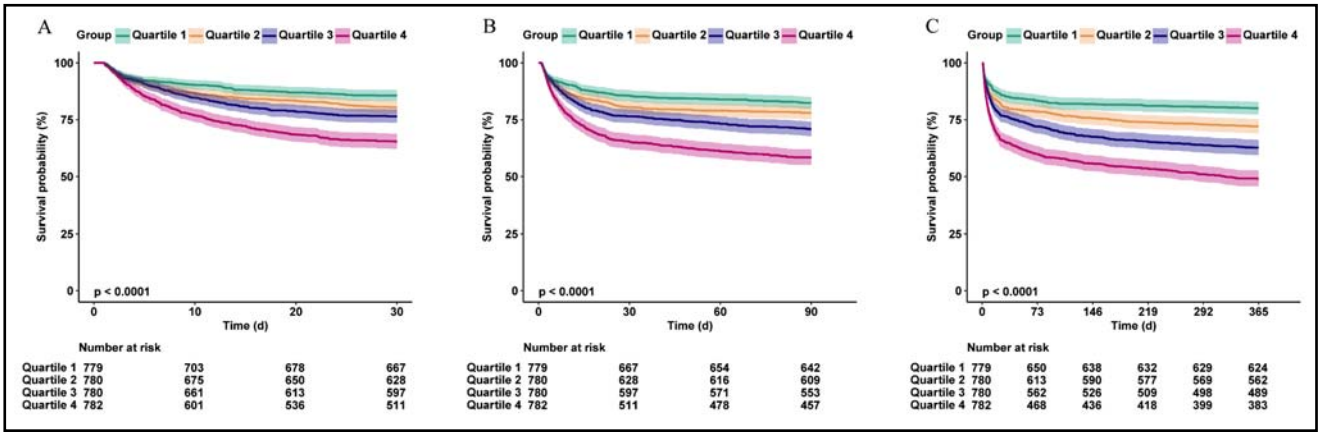

Fig. 2. Kaplan–Meier curves for 30-day (A), 90-day (B), and 1-year (C) survival of hemorrhagic stroke patients according to the ePWV levels. Abbreviations: ePWV, estimated pulse wave velocity.

≥ 12.66. Overall, the mean age of all participants was 66.2 ± 15.9 years, with males accounting for 51.2%. Patients with a higher ePWV level tended to have higher values of SOFA, CCI, MAP, BUN, and creatinine. They also had lower GCS, SpO_2, WBC, and platelet. Patients in the higher ePWV quartile group tended to have atrial fibrillation, myocardial infarct, and renal disease. The overall 30-day, 90-day, and 1-year mortality rates were 23.0%, 27.6%, and 34.1%, respectively. Additionally, participants with a higher ePWV level had higher 30-day, 90-day, and 1-year mortality.

Effect of ePWV on outcomes

As illustrated by the Kaplan–Meier curves, ePWV levels showed a strong relation with 30-day, 90-day, and 1-year survival in univariable analysis (p values for all log-rank tests < 0.001, Fig. 2). In Table 2, we show both the unadjusted model and the adjusted models of Cox regression. In Model 1 (the unadjusted model) and Model 2 (the minimally-adjusted model), elevated ePWV was positively associated with 30-day all-cause mortality. Even after adjusting for all potential confounders (Model 3), the relationship remained significant with ePWV considered as a continuous variable (hazard ratio [HR], 95% confidence interval [CI]: 1.21 [1.16, 1.26]; $p < 0.001$). A similar relationship was also found for 90-day mortality and 1-year mortality. In model 3, higher ePWV was independently associated with increased 90-day (HR, 95% CI: 1.20 [1.16, 1.25]; $p < 0.001$) and 1-year (HR, 95% CI: 1.18 [1.15, 1.22]; $p < 0.001$) mortality. ePWV was also treated as a categorical variable (four quartiles), with the first quartile serving as the reference group for comparisons to other groups. For 30-day mortality, in the fully-adjusted model, the HR with 95% CI for the second, third, and fourth quartile groups were 1.40 (1.07, 1.83), 1.82 (1.37, 2.42), and 3.15 (2.30, 4.32), respectively, when compared to the reference group (p for trend < 0.001). A similar trend was also found for 90-day mortality and 1-year mortality. Using restricted cubic spline analyses, linear relationships were found between ePWV and 30-day, 90-day,

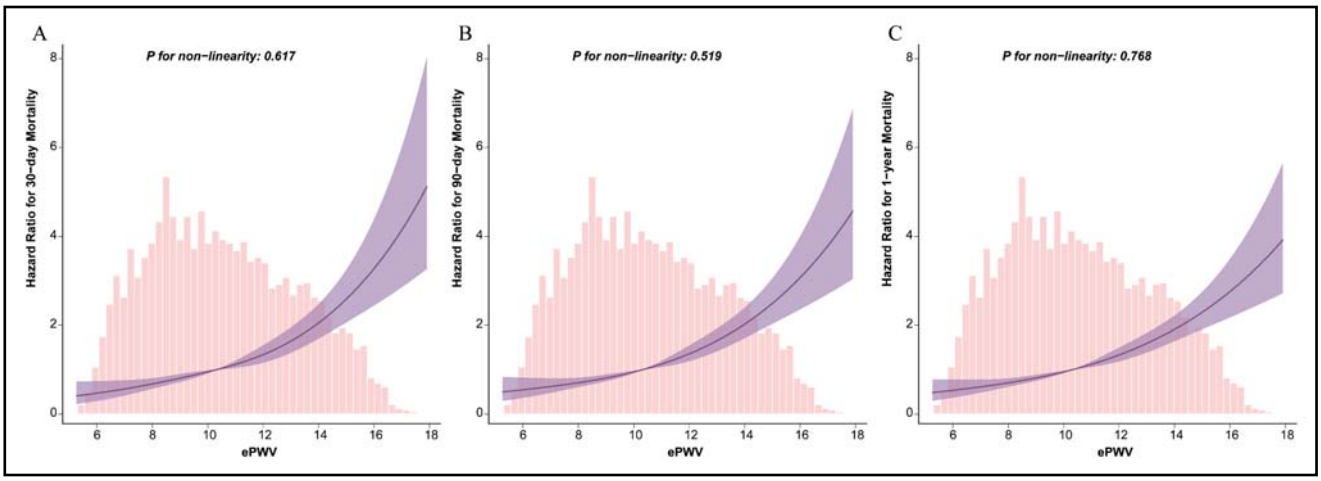

Fig. 3. Multivariable-adjusted restricted cubic spline analyses of association between ePWV and 30-day (A), 90-day (B), and 1-year (C) all-cause mortality. The purple lines depict the estimated risk of mortality, and the shaded areas represent the 95% CI. HRs were adjusted for all the covariates of Model 3 in Table 2. Abbreviations: ePWV, estimated pulse wave velocity; CI, confidence interval; HR, hazard ratio.

Tab. 2. Relationship between ePWV and all-cause mortality among hemorrhagic stroke patients

	Model 1		Model 2		Model 3	
	HR (95% CI)	***p*-Value**	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
30-day mortality						
ePWV	1.16 (1.12, 1.19)	< 0.001	1.17 (1.14, 1.20)	< 0.001	1.21 (1.16, 1.26)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.39 (1.09, 1.78)	0.008	1.44 (1.13, 1.84)	0.004	1.40 (1.07, 1.83)	0.015
Quartile 3	1.70 (1.35, 2.16)	< 0.001	1.75 (1.38, 2.22)	< 0.001	1.82 (1.37, 2.42)	< 0.001
Quartile 4	2.69 (2.16, 3.35)	< 0.001	2.91 (2.33, 3.63)	< 0.001	3.15 (2.30, 4.32)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
90-day mortality						
ePWV	1.16 (1.14, 1.19)	< 0.001	1.17 (1.15, 1.20)	< 0.001	1.20 (1.16, 1.25)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.29 (1.03, 1.61)	0.027	1.32 (1.06, 1.66)	0.015	1.25 (0.98, 1.60)	0.079
Quartile 3	1.75 (1.42, 2.17)	< 0.001	1.79 (1.45, 2.21)	< 0.001	1.70 (1.32, 2.20)	< 0.001
Quartile 4	2.73 (2.23, 3.33)	< 0.001	2.90 (2.37, 3.55)	< 0.001	2.81 (2.11, 3.73)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
1-year mortality						
ePWV	1.18 (1.15, 1.20)	< 0.001	1.19 (1.16, 1.21)	< 0.001	1.18 (1.15, 1.22)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.47 (1.19, 1.80)	< 0.001	1.50 (1.22, 1.84)	<0.001	1.35 (1.08, 1.69)	0.008
Quartile 3	2.05 (1.68, 2.49)	< 0.001	2.08 (1.71, 2.52)	<0.001	1.81 (1.43, 2.28)	< 0.001
Quartile 4	3.11 (2.59, 3.75)	< 0.001	3.26 (2.70, 3.93)	<0.001	2.79 (2.16, 3.61)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Note: Model 1 was adjusted for none; Model 2 was adjusted for sex and race; Model 3 was further adjusted for hypertension, atrial fibrillation, myocardial infarct, CPD, diabetes, renal disease, liver disease, malignant tumor, SOFA, APS III, GCS, CCI, HR, RR, SpO2, temperature, hemoglobin, RDW, WBC, platelet, anion gap, bicarbonate, BUN, creatinine, glucose, INR, PT, PTT, MV, RRT, vasopressors, and neurosurgery.

Abbreviations: ePWV, estimated pulse wave velocity; HR, hazard ratio; CI, confidence interval; CPD, chronic pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; GCS, Glasgow coma scale; CCI, Charlson comorbidity index; HR, heart rate; RR, respiratory rate; SpO2, saturation of pulse oximetry; RDW, red cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; MV, mechanical ventilation; RRT, renal replacement therapy.

and 1-year mortality among critically ill patients with hemorrhagic stroke (Fig. 3).

Subgroup analyses and sensitivity analysis

Subgroup and interaction analyses were conducted to ensure that the association between 30-day mortality and ePWV remained consistent. Interaction analyses revealed statistically significant interactions for race, vasopressors, and MV (Fig. 4). However, the results in each subgroup population remained consistent with the primary analysis in these stratified variables. Considering the overlapping 95% CIs and the consistent directional associations observed across all subgroups, the interaction test results may lack substantial clinical implications. After excluding the participants with incomplete covariate data, we reanalyzed the association between ePWV and outcomes and found that the Cox regression results remained robust (Table S2).

ROC curve analyses

The predictive performance of ePWV and severity scores for 30-day, 90-day, and 1-year mortality are shown in Table S3. The predictive values of ePWV, severity scores, and their combinations for 30-day mortality were visualized by the ROC curves in Fig. 5. For 30-day mortality, the AUROCs of ePWV, SOFA, and APS III were 0.627, 0.704, and 0.709, respectively. Compared to SOFA or APS III alone, the AUROC

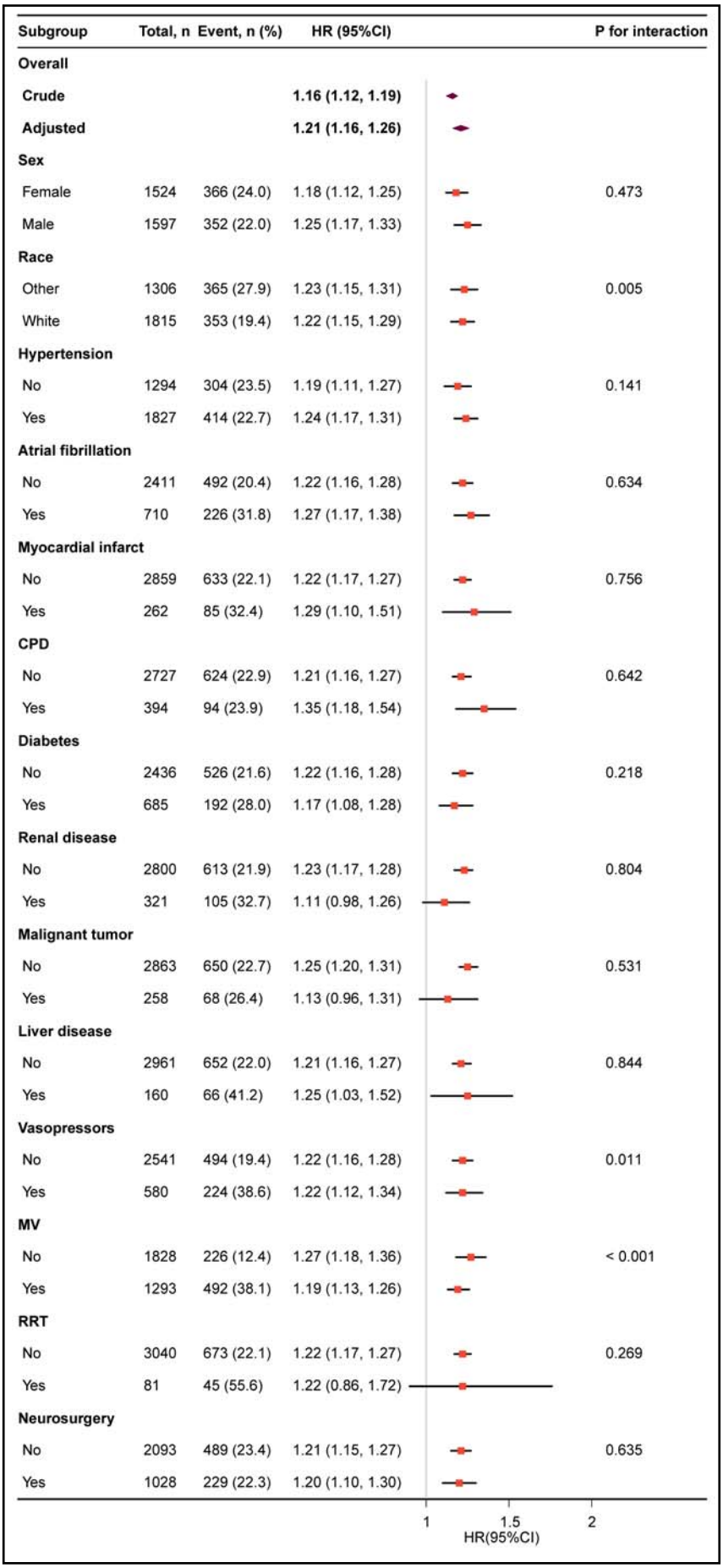

Fig. 4. Stratified analyses of the relationships between ePWV and 30-day mortality (adjusted for the covariates according to Model 3 in Table 2). Abbreviations: ePWV, estimated pulse wave velocity; HR, hazard ratio; CI, confidence interval; CPD, chronic pulmonary disease; MV, mechanical ventilation; RRT, renal replacement therapy.

of each severity score combined with ePWV was significantly elevated in predicting 30-day mortality (all p values for the DeLong test < 0.001). Similar findings were found for 90-day mortality and 1-year mortality.

DISCUSSION

To the best of our knowledge, this is the first study to explore the relationship between ePWV and mortality among critically ill patients with hemorrhagic stroke. We identified a positive correlation between ePWV level and the risk of mortality in hemorrhagic stroke patients, even after adjusting for potential confounders. Subgroup analyses and the sensitivity analysis confirmed the robustness of our results. We also found that the effect of ePWV on mortality is linear in hemorrhagic stroke patients. Furthermore, when compared to SOFA or APS III individually, the AUROC of each scoring system combined with ePWV was significantly higher in predicting mortality. These results will deepen the understanding of the relationship between ePWV and mortality in ICU patients with hemorrhagic stroke, enhancing physicians' ability to risk-stratify patients and improve therapy decisions. Compared to some disease severity score systems, ePWV is more objective and accessible, making it directly applicable for prognosis evaluation.

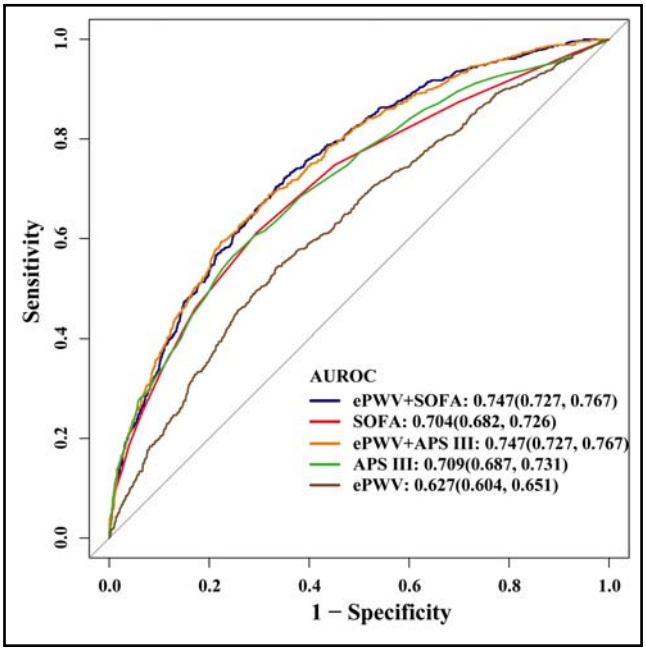

Fig. 5. ROC curve analyses for ePWV, SOFA, APS III, and their combinations based on 30-day mortality. Abbreviations: ROC, receiver operating characteristic; ePWV, estimated pulse wave velocity; SOFA, sequential organ failure assessment; APS III, acute physiology score III; AUROC, area under the receiver operating characteristic curve.

The measurement of carotid-femoral PWV (cfPWV) is widely regarded as the gold standard for evaluating arterial stiffness and vascular aging (Heffernan *et al.* 2023; Townsend *et al.* 2015). Despite ongoing efforts to develop affordable and easy-to-use devices, the current measurement of cfPWV still necessitates the use of costly equipment, well-trained operators, and a prolonged testing duration (Greve *et al.* 2017). ePWV calculated based on chronological age and MAP has been shown in some studies to have comparable performance to actual cfPWV measurements and is considered a reliable biomarker of cardiovascular risk (Hametner *et al.* 2021; Prelević *et al.* 2024). Recently, the prognostic value of vascular aging biomarkers, including cfPWV and ePWV, has been found in the field of cerebrovascular diseases. A study conducted by Samara *et al.* suggested that cfPWV is an independent predictor of all-cause mortality and cardiovascular events in patients with first-ever acute stroke (Samara *et al.* 2022). Huang *et al.* explored the relationship between ePWV and all-cause as well as cardio-cerebrovascular disease mortality in the stroke population and found that an elevated ePWV level is associated with higher mortality in stroke patients (Huang *et al.* 2023). Higher ePWV levels have also been shown to be associated with increased mortality in critically ill patient populations, including acute kidney injury, coronary heart disease, and chronic kidney disease complicated with atherosclerotic heart disease (Cui *et al.* 2024, 2024; Gu *et al.* 2024). Additionally, a similar linear dose-response relationship between ePWV and mortality was observed in the two aforementioned studies (Cui *et al.* 2024, 2024). The study conducted by Gu *et al.* also indicated that incorporating ePWV significantly improved the prediction performance for all-cause mortality across various scoring systems (Gu *et al.* 2024). Our results in ICU patients with hemorrhagic stroke were in line with above-mentioned studies. Although our study identified a significant positive association between ePWV and outcomes, the underlying mechanisms remain to be elucidated.

Several potential mechanisms may underlie the association between ePWV and mortality in critically ill patients with hemorrhagic stroke. One possible mechanism is that the degree of arterial stiffness represented by ePWV levels may be related to systemic inflammation (Vlachopoulos *et al.* 2005; Yiu *et al.* 2011), and inflammation is significantly pronounced in patients with stroke, particularly in those with hemorrhagic stroke. Elevated levels of systemic inflammation are associated with higher mortality in hemorrhagic stroke (Göçmen & Gesoglu Demir, 2024). Another possibility is that the early ePWV after ICU admission is directly influenced by the blood pressure value according to the ePWV calculation formula. PWV is also influenced both chronically and acutely by blood pressure (Heffernan *et al.* 2023). As a result, it is not surprising that patients with a higher ePWV level tended to have higher MAP values in our study cohort. Elevated blood pressure levels are associated with a higher risk of mortality and poorer clinical outcomes in acute hemorrhagic stroke patients, and this effect may be attributed to hematoma enlargement, and elevated blood pressure levels are also

considered a physiological response to increased intracranial pressure (Maida *et al.* 2017). It is noteworthy that patients in the quartile 1 category had lower levels of MAP compared to patients in the other categories. In general, excessively low blood pressure may be present in a pathological state such as shock, indicating impaired vascular function and poor tissue perfusion, which can result in higher mortality (Drolz & Fuhrmann, 2021; Markwart *et al.* 2020). However, ePWV is linearly related to all-cause mortality in our study cohort, and patients in the quartile 1 category had the lowest mortality. Therefore, another potential mechanism is required to elucidate the findings and avoid misleading conclusions. Chronological age serves as the principal determinant of central arterial stiffness (Benetos *et al.* 2001), and there is a strong correlation between age and ePWV (Möstl *et al.* 2022). In our study, we observed significant differences in the age of patients across quartile categories, and patients in the quartile 1 category had the lowest mean age. Consequently, it is not difficult to understand that patients in the quartile 1 category may exhibit a higher survival rate attributable to their younger age, despite having a lower MAP. Also, our findings may also be explained by genetic predisposition. Arterial function and mortality have genetic predispositions, as evidenced by the strong associations between vascular biomarkers and genetic indicators of biological aging and life expectancy (Benetos *et al.* 2001; Lacolley *et al.* 2017). Lastly, due to the intricate and dynamic relationship between age and blood pressure, both in acute settings and over the lifespan, ePWV may be capturing distinct elements of arterial stiffness that are related to but also differ from cfPWV (Heffernan *et al.* 2023). ePWV potentially encompasses a diverse array of biological information that may influence patient prognosis. Further research is needed to elucidate the clinical significance and value of ePWV in medical practice.

Our study has some limitations and pitfalls. Firstly, as a single-center retrospective study, this study may have limitations regarding the generalizability of the conclusions. Secondly, the MIMIC-IV database did not contain information on the cause of death, which limited further analyses of the relationship between ePWV and prognosis among critically ill patients with hemorrhagic stroke. Finally, ePWV is a mathematical representation that incorporates both MAP and age rather than being a direct measurement of PWV. Thus, the ePWV may not accurately reflect the extent of vascular aging. Notwithstanding the aforementioned shortcomings, our study offers valuable insights into the relationship between ePWV and prognosis in critically ill patients with hemorrhagic stroke.

CONCLUSIONS

The current study revealed that a higher level of early ePWV is significantly associated with increased all-cause mortality in critically ill patients with hemorrhagic stroke. These findings may offer healthcare professionals a promising prognostic marker for early intervention and clinical planning. Further research is needed to evaluate the prognostic value of ePWV among critically ill patients with hemorrhagic stroke as well as in other clinical settings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The IRBs of both MIT and BIDMC approved the utilization of the database for research purposes. The corresponding author, Duo Yang, has successfully completed the training on "Human Subject Protection" and has been granted access to this database (Certification Number: 48247201). Informed consents were waived as the patient information in this database was anonymized. Additionally, our study strictly adhered to all pertinent ethical regulations concerning data usage.

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AUTHORS' CONTRIBUTIONS

QL wrote the original manuscript. HZ and SY prepared the figures. XS and RL conducted the data analyses. ZH conducted the study design. LZ reviewed the manuscript. DY performed the data extraction and reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA AVAILABILITY

All the data used to support this study are available from the corresponding author upon request.

SUPPLEMENTARY INFORMATION

Table S1 Univariable Cox regression analysis of covariates and 30-day mortality. Table S2 Relationship between ePWV and all-cause mortality after excluding participants with incomplete data of covariates. Table S3 Performance of ePWV and severity scores in predicting 30-day, 90-day and 1-year mortality.

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SUPPLEMENTARY TABLES

Supp. Tab. 1. Univariable Cox regression analysis of covariates and 30-day mortality

Variables	HR (95% CI)	*p*-Value
Sex		
Female	1.00 (Reference)	
Male	0.90 (0.78, 1.05)	0.179
Race		
Other	1.00 (Reference)	
White	0.66 (0.57, 0.76)	< 0.001
Hypertension		
No	1.00 (Reference)	
Yes	0.96 (0.83, 1.11)	0.562
Atrial fibrillation		
No	1.00 (Reference)	
Yes	1.64 (1.40, 1.92)	< 0.001
Myocardial infarct		
No	1.00 (Reference)	
Yes	1.55 (1.24, 1.95)	< 0.001
CPD		
No	1.00 (Reference)	
Yes	1.03 (0.83, 1.28)	0.781
Diabetes		
No	1.00 (Reference)	
Yes	1.34 (1.14, 1.58)	< 0.001
Renal disease		
No	1.00 (Reference)	
Yes	1.58 (1.28, 1.94)	< 0.001
Liver Disease		
No	1.00 (Reference)	
Yes	2.04 (1.58, 2.62)	< 0.001
Malignant tumor		
No	1.00 (Reference)	
Yes	1.15 (0.89, 1.47)	0.284
SOFA	1.21 (1.19, 1.24)	< 0.001
APS III	1.03 (1.03, 1.04)	< 0.001
GCS	0.89 (0.87, 0.91)	< 0.001
CCI	1.14 (1.11, 1.17)	< 0.001
HR (bpm)	1.03 (1.02, 1.03)	< 0.001
RR (bpm)	1.12 (1.10, 1.14)	< 0.001
SpO_2 (%)	1.12 (1.08, 1.17)	< 0.001
Temperature (°C)	1.39 (1.17, 1.66)	< 0.001
Hemoglobin (g/dL)	0.85 (0.82, 0.88)	< 0.001
RDW (%)	1.21 (1.17, 1.25)	< 0.001
WBC ($\times 10^9$/L)	1.0094 (1.0058, 1.0131)	< 0.001
Platelet ($\times 10^9$/L)	0.9963 (0.9953, 0.9974)	< 0.001
Anion gap (mmol/L)	1.09 (1.07, 1.12)	< 0.001
Bicarbonate (mmol/L)	0.95 (0.92, 0.97)	< 0.001
BUN (mg/dL)	1.02 (1.01, 1.02)	< 0.001
Creatinine (mg/dL)	1.09 (1.06, 1.12)	< 0.001
Glucose (mg/dL)	1.0061 (1.0051, 1.0071)	< 0.001
INR	1.71 (1.52, 1.92)	< 0.001
PT (s)	1.02 (1.02, 1.03)	< 0.001
PTT (s)	1.01 (1.01, 1.02)	< 0.001
MV		
No	1.00 (Reference)	
Yes	3.68 (3.15, 4.31)	< 0.001
RRT		
No	1.00 (Reference)	
Yes	2.79 (2.07, 3.78)	< 0.001
Vasopressors		
No	1.00 (Reference)	
Yes	2.26 (1.93, 2.65)	< 0.001
Neurosurgery		
No	1.00 (Reference)	
Yes	0.92 (0.79, 1.08)	0.326

Abbreviations: HR, hazard ratio; CI, confidence interval; CPD, chronic pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; GCS, Glasgow coma scale; CCI, Charlson comorbidity index; HR, heart rate; RR, respiratory rate; SpO2, saturation of pulse oximetry; RDW, red cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; MV, mechanical ventilation; RRT, renal replacement therapy.

Supp. Tab. 2. Relationship between ePWV and all-cause mortality after excluding participants with incomplete data of covariates

	Model 1		Model 2		Model 3	
	HR (95% CI)	***p*-Value**	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
30-day mortality						
ePWV	1.15 (1.12, 1.19)	< 0.001	1.17 (1.13, 1.20)	< 0.001	1.21 (1.16, 1.26)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.44 (1.12, 1.86)	0.004	1.49 (1.16, 1.92)	0.002	1.44 (1.09, 1.90)	0.009
Quartile 3	1.66 (1.30, 2.12)	< 0.001	1.70 (1.33, 2.18)	< 0.001	1.76 (1.31, 2.36)	< 0.001
Quartile 4	2.77 (2.20, 3.47)	< 0.001	2.99 (2.37, 3.76)	< 0.001	3.26 (2.36, 4.51)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
90-day mortality						
ePWV	1.16 (1.14, 1.20)	< 0.001	1.17 (1.14, 1.21)	< 0.001	1.20 (1.16, 1.25)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.28 (1.02, 1.62)	0.036	1.32 (1.04, 1.66)	0.020	1.25 (0.97, 1.61)	0.082
Quartile 3	1.71 (1.37, 2.13)	< 0.001	1.74 (1.40, 2.17)	< 0.001	1.67 (1.29, 2.18)	< 0.001
Quartile 4	2.77 (2.26, 3.40)	< 0.001	2.94 (2.39, 3.62)	< 0.001	2.93 (2.19, 3.93)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
1-year mortality						
ePWV	1.18 (1.15, 1.21)	< 0.001	1.19 (1.16, 1.21)	< 0.001	1.19 (1.15, 1.23)	< 0.001
ePWV quartiles						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.42 (1.15, 1.76)	0.001	1.45 (1.17, 1.80)	0.001	1.32 (1.05, 1.66)	0.018
Quartile 3	1.97 (1.61, 2.41)	< 0.001	2.00 (1.64, 2.45)	< 0.001	1.75 (1.38, 2.22)	< 0.001
Quartile 4	3.15 (2.60, 3.81)	< 0.001	3.29 (2.71, 3.98)	< 0.001	2.86 (2.20, 3.73)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

Note: Model 1 was adjusted for none; Model 2 was adjusted for sex and race; Model 3 was further adjusted for hypertension, atrial fibrillation, myocardial infarct, CPD, diabetes, renal disease, liver disease, malignant tumor, SOFA, APS III, GCS, CCI, HR, RR, SpO2, temperature, hemoglobin, RDW, WBC, platelet, anion gap, bicarbonate, BUN, creatinine, glucose, INR, PT, PTT, MV, RRT, vasopressors, and neurosurgery.

Abbreviations: ePWV, estimated pulse wave velocity; HR, hazard ratio; CI, confidence interval; CPD, chronic pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; GCS, Glasgow coma scale; CCI, Charlson comorbidity index; HR, heart rate; RR, respiratory rate; SpO2, saturation of pulse oximetry; RDW, red cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; MV, mechanical ventilation; RRT, renal replacement therapy.

Supp. Tab. 3. Performance of ePWV and severity scores in predicting 30-day, 90-day and 1-year mortality

Variables	**30-day mortality**		**90-day mortality**		**1-year mortality**	
	AUROC (95% CI)	***p*-Value**	**AUROC (95% CI)**	***p*-Value**	**AUROC (95% CI)**	***p*-Value**
ePWV	0.627 (0.604, 0.651)		0.638 (0.617, 0.660)		0.657 (0.636, 0.677)	
SOFA	0.704 (0.682, 0.726)	< 0.001	0.700 (0.679, 0.720)	< 0.001	0.685 (0.666, 0.705)	< 0.001
SOFA + ePWV	0.747 (0.727, 0.767)		0.749 (0.731, 0.768)		0.745 (0.727, 0.763)	
APS III	0.709 (0.687, 0.731)	< 0.001	0.714 (0.693, 0.735)	< 0.001	0.703 (0.683, 0.722)	< 0.001
APS III + ePWV	0.747 (0.727, 0.767)		0.756 (0.737, 0.774)		0.751 (0.734, 0.769)	

Abbreviations: ePWV, estimated pulse wave velocity; AUROC: area under the receiver operating characteristic curve; CI, confidence interval; SOFA, sequential organ failure assessment; APS III, acute physiology score III.