

Association of estimated pulse wave velocity with 28-day mortality in sepsis: A MIMIC-IV study

Xiuxiu Ding^{*1} MMed, Chaochao Wei^{*1,2,3} MMed, Shuang Cai¹ MMed, Bingli Zhang¹ MMed, Jiwei Li¹ MMed, Dajia Fu^{4,5} MM

ABSTRACT

Introduction: Despite the association between sepsis and carotid-femoral pulse wave velocity, the relationship between estimated pulse wave velocity (ePWV) and sepsis remains unclear. This study investigated the correlation between ePWV and 28-day mortality in patients with sepsis.

Methods: Using data from the Medical Information Mart for Intensive Care IV database between 2008 and 2019, the association between ePWV and 28-day mortality was analysed with Kaplan-Meier curves, Cox models, and restricted cubic splines (RCS). Subgroup analysis was performed to validate the findings. A combined model was constructed by screening variables via Cox-least absolute shrinkage and selection operator (LASSO), with its incremental predictive value evaluated using receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

Results: Survival analysis showed an inverse association between ePWV and survival rates (log-rank test $P < 0.001$). Cox analysis demonstrated that each increase in ePWV was associated with a significantly higher risk of 28-day mortality in patients with sepsis (hazard ratio 1.905, 95% confidence interval 1.672–2.169, $P < 0.001$), with linearity confirmed by RCS analysis ($P_{\text{nonlinear}} = 0.3313$). Subgroup analysis indicated significant interaction effects of invasive ventilation ($P_{\text{interaction}} < 0.001$) and a history of malignant tumours ($P_{\text{interaction}} = 0.005$) on mortality. The combined model optimised by LASSO demonstrated the best discriminative performance (ROC=0.823) and an improved net clinical benefit with the inclusion of ePWV, as confirmed by DCA.

Conclusion: ePWV was linearly and positively correlated with the risk of 28-day mortality in patients with sepsis.

Keywords: 28-day mortality, ePWV, MIMIC-IV, sepsis

INTRODUCTION

Among patients in intensive care units (ICUs), sepsis is a major cause of mortality.¹ In 2017, a disease burden study showed that there were approximately 48.9 million cases of sepsis worldwide, with 11

CLINICAL IMPACT

What is New

- Estimated pulse wave velocity (ePWV) is significantly positively correlated with 28-day mortality in patients with sepsis.
- Invasive ventilation and a history of malignancy influence the association between ePWV and 28-day mortality in patients with sepsis.

Clinical Implications

- ePWV may serve as a potential indicator for assessing the prognosis of patients with sepsis, aiding in the early identification of high-risk individuals in clinical practice and providing a reference for personalised management and prognostic evaluation.

million deaths, accounting for 19.7% of the total global mortality. Although the age-standardised incidence rate decreased by 37.0% and the mortality rate decreased by 52.8% compared to 1990, sepsis remains a major factor contributing to the global health burden.² Sepsis, which is characterised by systemic inflammatory responses that can escalate to organ dysfunction, significantly increases the risk of cardiovascular disease (CVD), including myocardial infarction, acute coronary syndrome, congestive heart failure, and atherosclerosis.^{3–5} Therefore, monitoring the risk of CVD and atherosclerosis in patients with sepsis is critical.

An independent predictor of CVD mortality, carotid-femoral pulse wave velocity (cf-PWV) is the gold standard for assessing arterial stiffness.⁶ A recent study also found a relationship between cf-PWV and sepsis, with higher levels associated with poorer survival in patients with sepsis.⁷ These data indicate that monitoring variations in cf-PWV may aid in

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¹ Department of Respiratory and Critical Care Medicine, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

² Department of Oncology, Xiangya Hospital Central South University, China

³ NHC Key Laboratory of Tropical Disease Control, Hainan Medical University, China

⁴ Department of Emergency Medicine, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

⁵ Department of Electrophysiology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

* Joint first authors

Correspondence: Dr Dajia Fu, Department of Emergency Medicine, and Electrophysiology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, No. 19 Xiuhua Road, Xiuying District, Haikou City, Hainan Province, 570311, China. Email: dajiafu666@163.com

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predicting mortality risk in patients with sepsis. However, the clinical utility of cf-PWV is limited because it requires specific equipment and qualified personnel to measure.⁸ Estimated pulse wave velocity (ePWV) is a simple measure derived from mean blood pressure (MBP) and chronological age.⁹ Evidence suggests that ePWV has predictive value comparable to that of pulse wave velocity (PWV), with a risk prediction difference of -0.3% compared with cf-PWV and PWV in evaluating CVD risk in the Danish MONICA10 cohort.^{10,11}

Although recent research has initially explored the association between ePWV and sepsis outcomes using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database,¹² uncertainties persist regarding the precise nature of this relationship and its incremental predictive value beyond conventional clinical models, owing to differences in study designs and analytical approaches. Consequently, the present study aimed to further elucidate the correlation between ePWV and 28-day mortality in patients with sepsis through an independent, rigorous analysis and to investigate in depth the potential factors influencing this association.

METHODS

Data source

Data were obtained from the publicly accessible MIMIC-IV database (<https://mimic.mit.edu/>),¹³ which

comprises data on ICU-admitted patients at Beth Israel Deaconess Medical Center in Boston from 2008 to 2019. MIMIC-IV is publicly available and anonymised; thus, no ethical approval was necessary.

Study population

The study included patients diagnosed with sepsis or septic shock using Sepsis-3 criteria.¹⁴ Data were collected from 2008 to 2019. Exclusion criteria included (1) children <18 years old; (2) patients with multiple ICU admissions (only the first admission was included); and (3) patients with ICU stays shorter than 1 day. A total of 19,422 eligible patients were included, of whom 16,414 survived within 28 days of ICU admission, and 3008 died during the same period (Fig. 1).

ePWV assessment and primary endpoint

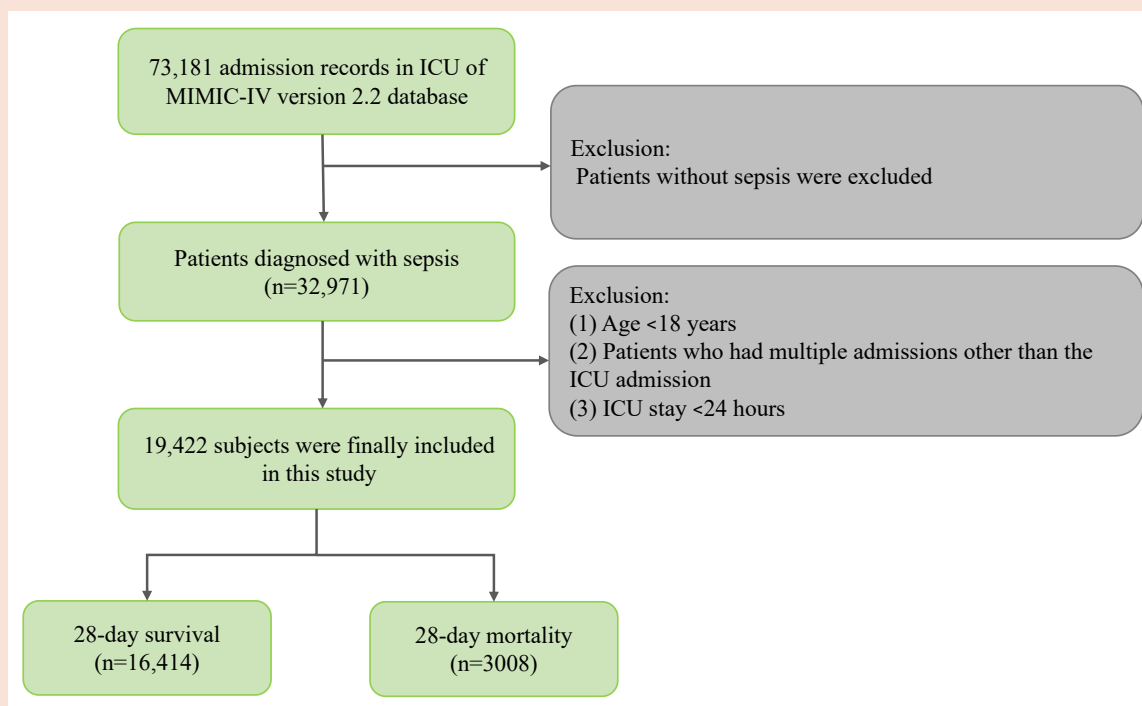
ePWV was computed using age and MBP with the formula from Greve et al.,¹¹ where $PWV = 9.587 - 0.402 \times \text{age} + 4.560 \times 10^{-3} \times \text{age}^2 - 2.621 \times 10^{-5} \times \text{age}^2 \times MBP + 3.176 \times 10^{-3} \times \text{age} \times MBP - 1.832 \times 10^{-2} \times MBP$. MBP was computed from diastolic blood pressure (DBP) and systolic blood pressure (SBP) as $MBP = DBP + 0.4 \times (SBP - DBP)$.¹⁵

The primary endpoint was 28-day mortality among patients with sepsis admitted to the ICU.

Variable collection

The MIMIC-IV database was used to collect patient data, including demographics, severity scores,

Fig. 1. Flowchart of study population selection.



ICU: intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care IV

comorbidities, vital signs, laboratory tests, and therapy information. Vital-sign and laboratory-test variables with missing values for more than 20% of the overall sample were eliminated. Missing values in other variables were handled using the random forest (RF) approach from the “mice” package. Supplementary Table S1 contains details on the variables that were included and eliminated. Severity scores were collected within 24 hours after ICU admission, whereas vital signs and laboratory tests were taken during the first 24 hours, with the most severe measurement used for variables with multiple values.

Statistical analysis

Structured Query Language queries were used to obtain data from MIMIC-IV (version 2.2), which was then analysed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The “tableone” package was used to create a baseline table, which displayed continuous variables as mean (standard deviation), and compared groups using t-tests. Categorical variables were reported as percentages (%) and compared using chi-squared test. A 2-tailed $P < 0.05$ indicated statistical significance.

The “jskm” package was used to generate Kaplan-Meier survival curves based on ePWV quartiles in patients with sepsis, as well as to perform log-rank testing. Variance inflation factor (VIF) was used to assess collinearity across variables, with VIF values greater than 4 suggesting collinearity. After accounting for multicollinearity, Cox proportional hazards models were created using the “survey” and “survival” packages to investigate the association between ePWV and 28-day mortality in patients with sepsis. A Cox proportional hazards model was created for ePWV quartiles and 28-day mortality in patients with sepsis. A trend test was used to determine whether there was a trend between ePWV and 28-day mortality in patients with sepsis, with $P < 0.05$ indicating a significant difference.

In the fully adjusted model, the “ms” package was used to perform restricted cubic spline (RCS) analysis to investigate the nonlinear association between ePWV and the 28-day mortality in patients with sepsis. All categorical variables were subjected to interaction and subgroup analysis.

To evaluate the predictive value of ePWV for mortality risk in ICU patients, the authors constructed multivariable survival prediction models. Initially, 59 candidate variables were included based on clinical relevance and prior literature¹⁶: age, race, vital signs (e.g. respiratory rate, temperature, SpO_2), laboratory parameters (e.g. lactate, creatinine, electrolytes, coagulation indicators), severity scores (Simplified Acute Physiology Score [SAPS] II, Acute Physiology

Score III, Logistic Organ Dysfunction System, Oxford Acute Severity of Illness Score), Glasgow Coma Scale score, Charlson Comorbidity Index, mechanical ventilation, and vasoactive drug use. Given potential multicollinearity among high-dimensional clinical variables, variable selection employed Cox-least absolute shrinkage and selection operator (LASSO) regression. Using 10-fold cross-validation, the optimal λ was selected based on the λ_{1se} criterion to balance model stability and overfitting risk.¹⁷ The final multivariable Cox joint model was constructed based on the 30 selected variables. To assess the predictive value of ePWV, the ePWV-only model, the ePWV-adjusted model, and a combined model were constructed, with their discriminative ability compared using time-dependent receiver operating characteristic (ROC) curves with area under the curve (AUC) and clinical utility evaluated using decision curve analysis (DCA). Statistical analyses were performed in R, with significance set at 2-tailed $P < 0.05$.

RESULTS

Baseline characteristics

This study included 19,422 patients, with 16,414 survivors within 28 days and 3008 deaths during the same period, corresponding to a mortality rate of 15.5%. The baseline characteristics are shown in Table 1. The overall cohort had a mean age of 66.67 years (standard deviation [SD] 16.28), with 58.1% male. Comparative analysis indicated that the deceased group had substantially higher ePWV values (10.60 [SD 2.75] versus [vs] 9.97 [SD 2.63], $P < 0.001$), were older (70.53 years [SD 15.18] vs 65.96 years [SD 16.38], $P < 0.001$), and had longer ICU stays (6.33 days [SD 5.25] vs 5.25 days [SD 6.55], $P < 0.001$) than the survivors. Furthermore, compared to the survivor group, the deceased group showed substantially lower SBP, DBP, and MBP values, higher severity scores, and a higher incidence of comorbidities (all $P < 0.001$).

Relationship between ePWV and 28-day mortality in patients with sepsis

Further investigation was undertaken into the relationship between ePWV and 28-day mortality in patients with sepsis. Kaplan-Meier survival curves showed a decrease in 28-day survival rates for patients with sepsis as ePWV levels increased, with significant intergroup differences (log-rank test, $P < 0.001$) (Fig. 2A).

Covariates associated with 28-day mortality in sepsis were selected, and after eliminating variables with multicollinearity, 35 variables were used to build a Cox proportional hazards model (Supplementary Table S2). Table 2 shows that ePWV, a continuous variable, was significantly associated with an elevated 28-day

Table 1. Characteristics of patients admitted to the intensive care unit for the first time.

Characteristic	Total (n=19,422)	28-day survival (n=16,414)	28-day mortality (n=3008)	P value
ePWW	10.07 (2.66)	9.97 (2.63)	10.60 (2.75)	<0.001
Sex				0.006
Female	8140 (41.9)	6811 (41.5)	1329 (44.2)	
Male	11,282 (58.1)	9603 (58.5)	1679 (55.8)	
Age, years	66.67 (16.28)	65.96 (16.38)	70.53 (15.18)	<0.001
Race				<0.001
White	13,054 (67.2)	11,245 (68.5)	1809 (60.1)	
Black	1537 (7.9)	1307 (8.0)	230 (7.6)	
Other race	4831 (24.9)	3862 (23.5)	969 (32.2)	
Marital status				<0.001
Married	10,676 (55.0)	8878 (54.1)	1798 (59.8)	
Unmarried	8746 (45.0)	7536 (45.9)	1210 (40.2)	
LOS, days	5.42 (6.38)	5.25 (6.55)	6.33 (5.25)	<0.001
Heart rate, times/min	86.77 (15.96)	86.04 (15.46)	90.76 (17.98)	<0.001
SBP, mmHg	115.64 (15.06)	116.20 (14.78)	112.56 (16.17)	<0.001
DBP, mmHg	61.24 (10.16)	61.39 (10.05)	60.40 (10.68)	<0.001
MBP, mmHg	76.58 (10.05)	76.85 (9.89)	75.11 (10.77)	<0.001
Respiratory rate, times/min	19.59 (4.03)	19.25 (3.85)	21.44 (4.49)	<0.001
Temperature, °C	36.88 (0.61)	36.91 (0.55)	36.72 (0.86)	<0.001
SpO₂	97.03 (2.20)	97.15 (1.94)	96.36 (3.20)	<0.001
Glucose, mg/dL	324.15 (9033.27)	292.09 (8790.39)	499.10 (10257.69)	0.248
SAPS II	40.18 (14.11)	38.16 (12.82)	51.20 (15.61)	<0.001
SOFA	5.89 (3.47)	5.45 (3.10)	8.31 (4.30)	<0.001
APS III	49.61 (22.05)	46.17 (19.35)	68.37 (26.07)	<0.001
Anion gap, mmol/L	16.64 (5.27)	16.07 (4.81)	19.71 (6.49)	<0.001
Bicarbonate, mmol/L	21.16 (4.89)	21.52 (4.58)	19.21 (5.93)	<0.001
Chloride, mmol/L	106.70 (6.65)	106.85 (6.35)	105.88 (8.06)	<0.001
Haematocrit, µmol/L	29.66 (6.35)	29.66 (6.26)	29.65 (6.82)	0.945
Haemoglobin, g/dL	9.84 (2.14)	9.87 (2.10)	9.66 (2.30)	<0.001
Platelet, K/µL	177.20 (102.25)	177.69 (99.63)	174.54 (115.47)	0.121
Potassium, K/µL	4.64 (0.88)	4.60 (0.85)	4.86 (0.98)	<0.001
PTT, seconds	43.84 (29.49)	42.10 (27.62)	53.37 (36.67)	<0.001
INR	1.65 (1.16)	1.58 (1.04)	2.04 (1.59)	<0.001
PT, seconds	17.93 (11.78)	17.20 (10.58)	21.92 (16.35)	<0.001
Sodium, mEq/L	136.72 (5.35)	136.79 (5.16)	136.36 (6.26)	<0.001
BUN, mg/dL	30.48 (24.12)	28.48 (22.66)	41.43 (28.51)	<0.001
WBC, K/µL	15.75 (12.31)	15.37 (11.25)	17.84 (16.81)	<0.001

Table 1. Characteristics of patients admitted to the intensive care unit for the first time. (Cont'd)

Characteristic	Total (n=19,422)	28-day survival (n=16,414)	28-day mortality (n=3008)	P value
RBC, m/μL	3.28 (0.73)	3.29 (0.72)	3.22 (0.80)	<0.001
MCH, pg	29.81 (2.61)	29.80 (2.54)	29.87 (2.94)	0.181
MCHC, g/L	32.53 (1.68)	32.64 (1.63)	31.90 (1.78)	<0.001
MCV, fL	90.34 (7.00)	90.06 (6.76)	91.85 (7.99)	<0.001
RDW	15.38 (2.44)	15.18 (2.30)	16.49 (2.85)	<0.001
Creatinine, mg/dL	1.65 (1.64)	1.57 (1.62)	2.10 (1.70)	<0.001
Invasive ventilation				<0.001
No	8375 (43.1)	7302 (44.5)	1073 (35.7)	
Yes	11,047 (56.9)	9112 (55.5)	1935 (64.3)	
Dialysis				<0.001
No	18,470 (95.1)	15,776 (96.1)	2694 (89.6)	
Yes	952 (4.9)	638 (3.9)	314 (10.4)	
Vasopression				<0.001
No	18,098 (93.2)	15,665 (95.4)	2433 (80.9)	
Yes	1324 (6.8)	749 (4.6)	575 (19.1)	
Antibiotics				<0.001
No	2502 (12.9)	2009 (12.2)	493 (16.4)	
Yes	16,920 (87.1)	14,405 (87.8)	2515 (83.6)	
Congestive heart failure				<0.001
No	13,799 (71.0)	11,870 (72.3)	1929 (64.1)	
Yes	5623 (29.0)	4544 (27.7)	1079 (35.9)	
Peripheral vascular disease				0.001
No	17,119 (88.1)	14,521 (88.5)	2598 (86.4)	
Yes	2303 (11.9)	1893 (11.5)	410 (13.6)	
Chronic lung disease				<0.001
No	14,425 (74.3)	12,292 (74.9)	2133 (70.9)	
Yes	4997 (25.7)	4122 (25.1)	875 (29.1)	
Chronic kidney disease				<0.001
No	15,274 (78.6)	13,099 (79.8)	2175 (72.3)	
Yes	4148 (21.4)	3315 (20.2)	833 (27.7)	
Malignant tumour				<0.001
No	16,822 (86.6)	14,436 (87.9)	2386 (79.3)	
Yes	2600 (13.4)	1978 (12.1)	622 (20.7)	

APS III: Acute Physiology and Chronic Health Evaluation III; BUN: blood urea nitrogen; DBP: diastolic blood pressure; ePWV: estimated pulse wave velocity; INR: international normalised ratio; LOS: length of stay; MBP: mean blood pressure; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; RDW: red cell volume distribution width; SAPS II: Simplified Acute Physiology Score II; SBP: systolic blood pressure; SOFA: Sequential Organ Failure Assessment; SpO₂: peripheral oxygen saturation; WBC: white blood cell

Continuous variables are displayed as mean (standard deviation) and compared between groups using t-tests. Categorical variables are reported as percentages (%) and compared by chi-squared test. $P < 0.05$ indicates statistical significance. Variables having missing values greater than 20% of the overall sample size in vital signs and laboratory tests were eliminated. Missing values in other variables were handled with the Random Forest.

mortality in patients with sepsis in the fully adjusted model (hazard ratio [HR] 1.096, 95% confidence interval [CI] 1.076–1.115, $P < 0.001$). A multivariate-adjusted Cox proportional hazards model was created by classifying ePWV into quartiles. As shown in Table 2, increasing ePWV levels increased the risk of 28-day mortality in patients with sepsis across all 3 models ($P < 0.001$). In the fully adjusted model, the risk for Q2, Q3, and Q4 increased by 18.2% (HR 1.182, 95% CI 1.052–1.329, $P = 0.005$), 43.6% (HR 1.436, 95% CI 1.269–1.626, $P < 0.001$), and 90.5% (HR 1.905, 95% CI 1.672–2.169, $P < 0.001$), respectively, compared to Q1.

In the RCS analysis, an increase in ePWV was associated with an increase in 28-day mortality in patients with sepsis (P -overall < 0.0001), with no significant nonlinear association (P -nonlinear = 0.3313) (Fig. 2B).

Subgroup analysis of the relationship between ePWV and 28-day mortality in patients with sepsis

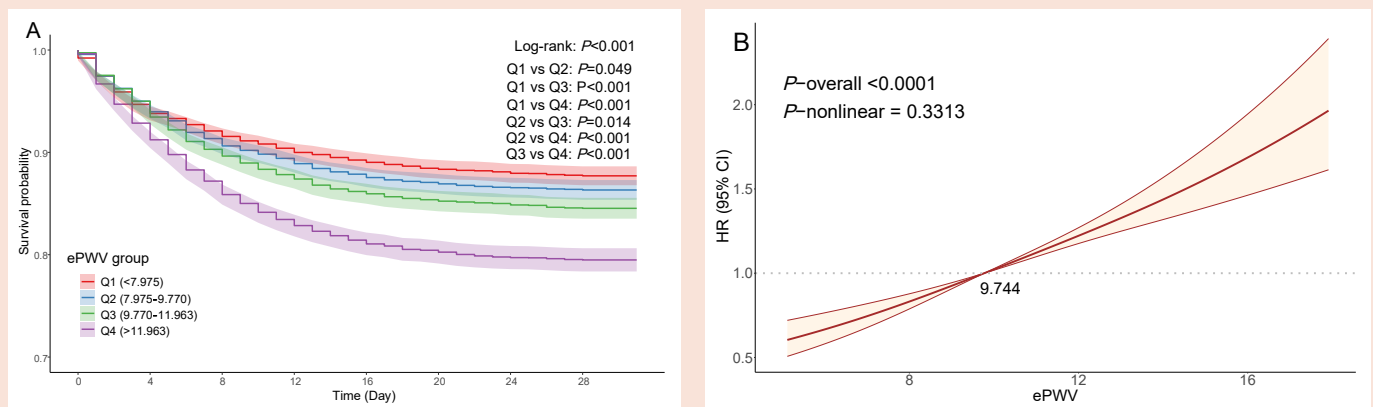
A subgroup analysis investigated other factors that influence the association between ePWV and 28-day mortality in patients with sepsis. As shown in Fig. 3, after controlling for all confounding factors, a significant association was detected between ePWV and the 28-day mortality risk in all patient subgroups except

Table 2. Association of ePWV with 28-day mortality in patients with sepsis.

Characteristic	HR (95% CI), P		
	Crude model	Model 1	Model 2
28-day mortality			
ePWV (continuous)	1.082 (1.068–1.096), < 0.001	1.088 (1.074–1.103), < 0.001	1.096 (1.076–1.115), < 0.001
ePWV (categorical)			
Q1 (< 7.975)	Ref	Ref	Ref
Q2 (7.975–9.770)	1.118 (1.001–1.248), 0.049	1.191 (1.066–1.331), 0.002	1.182 (1.052–1.329), 0.005
Q3 (9.770–11.963)	1.274 (1.144–1.419), < 0.001	1.369 (1.228–1.526), < 0.001	1.436 (1.269–1.626), < 0.001
Q4 (> 11.963)	1.740 (1.573–1.926), < 0.001	1.853 (1.228–1.526), < 0.001	1.905 (1.672–2.169), < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Note: Crude - unadjusted; Model 1 - adjusted for race, sex, marital status; Model 2 - adjusted for race, sex, marital status, Sequential Organ Failure Assessment, Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation III, heart rate, respiratory rate, temperature, SpO₂, glucose, anion gap, bicarbonate, chloride, platelet, potassium, partial thromboplastin time, international normalised ratio, prothrombin time, sodium, blood urea nitrogen, white blood cell, mean corpuscular haemoglobin concentration, red cell volume distribution width, creatinine, invasive ventilation, dialysis, vasopressin, antibiotics, congestive heart failure, peripheral vascular disease, chronic lung disease, chronic kidney disease, malignant tumour.

Fig. 2. Survival analysis and restricted cubic spline analysis. (A) Kaplan-Meier curve of 28-day survival rate in patients with sepsis at different ePWV levels. (B) Restricted cubic spline plot of the relationship between ePWV and 28-day mortality in patients with sepsis.



CI: confidence interval; ePWV: estimated pulse wave velocity; HR: hazard ratio

Black patients and patients with malignant tumours. Invasive ventilation use (P -interaction <0.001) and a history of malignancy (P -interaction = 0.005) showed significant interactions with mortality.

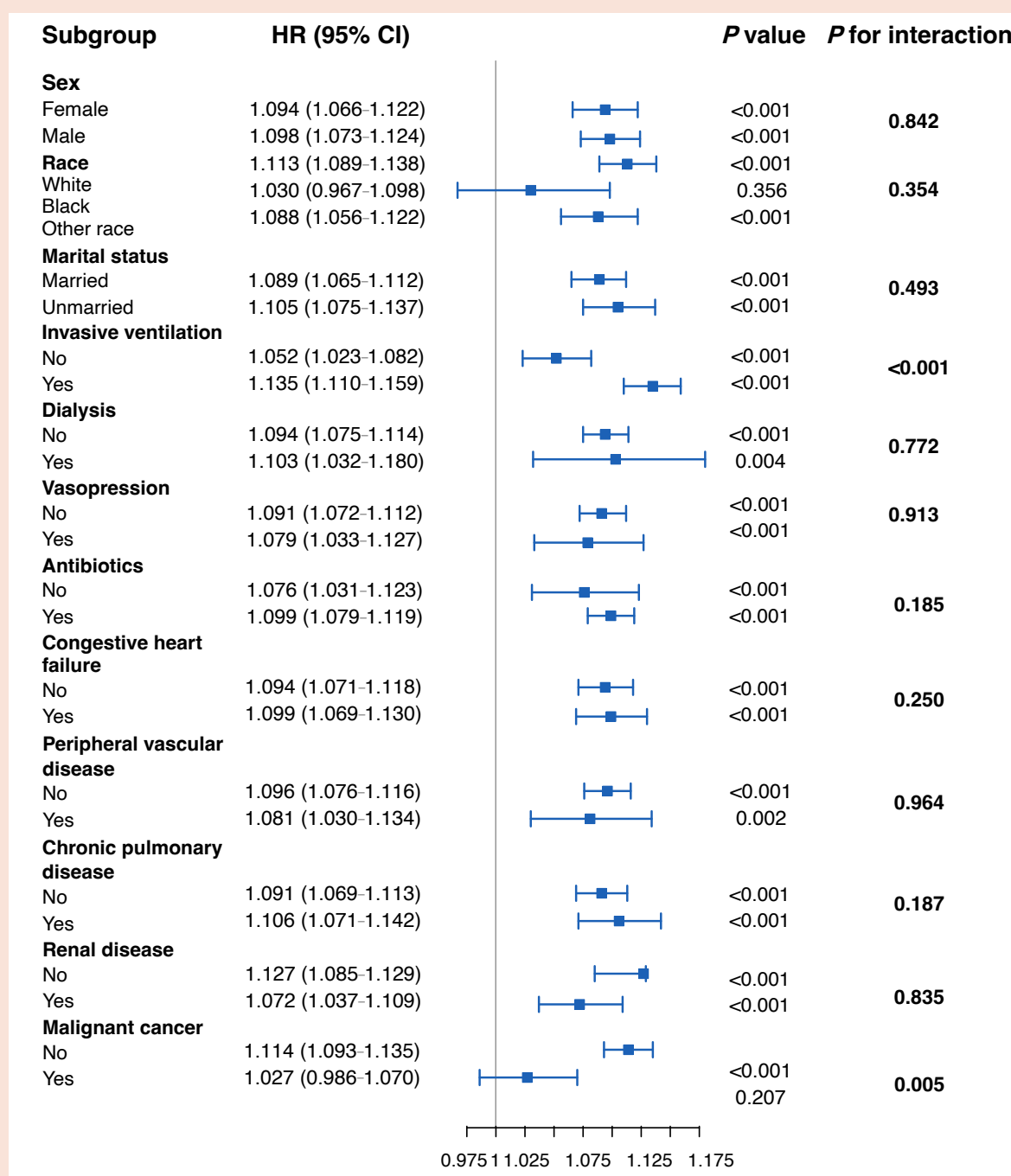
Evaluation of ePWV for predicting 28-day mortality in ICU patients

Using Cox-LASSO regression to screen 59 candidate variables, ePWV, together with traditional prognostic factors such as lactate, SAPS II score, and GCS score, was retained after determining the optimal penalty

parameter via cross-validation (Supplementary Fig. S1), indicating its independent predictive value in a multivariable context.

Time-dependent ROC analysis showed improvement in the AUC for 28-day mortality prediction from 0.567 for the ePWV-only model to 0.815 after adjusting for traditional clinical variables. The LASSO-optimised joint model achieved the highest discriminative ability, with an AUC of 0.823 (Fig. 4A), indicating that ePWV provides significant incremental prognostic value to the existing predictive framework. DCA showed

Fig. 3. Forest plot of subgroup analysis.



CI: confidence interval; HR: hazard ratio

that across a 20–80% risk threshold range, the joint model consistently yielded a higher net benefit than the ePWV-only model, adjusted model, or treat-all/treat-none strategies, with the advantage most pronounced in the intermediate-to-high risk range (Fig. 4B). This indicates that incorporating ePWV into existing predictive systems enhances clinical risk stratification.

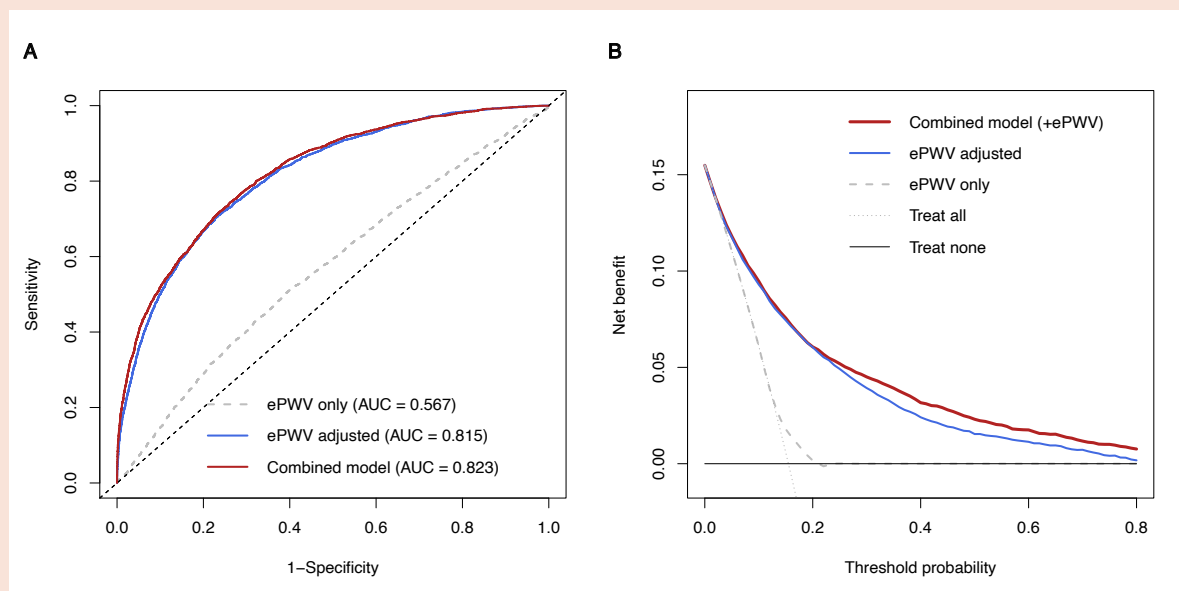
DISCUSSION

The findings show a positive correlation between ePWV and 28-day mortality in patients with sepsis, and this association is modified by the use of invasive ventilation and the absence of malignant tumours. The LASSO-optimised joint model exhibited optimal discriminative ability, with DCA confirming a significant improvement in net clinical benefit after the inclusion of ePWV.

The predictive value of ePWV as a simple clinical parameter for risk prediction in critically ill patients in the ICU has been established. ePWV is a reliable prognostic biomarker for critically ill patients with coronary artery disease, independently predicting short- and long-term mortality risk. Incorporating ePWV into standard risk assessments improves the predictive power of 1-year and in-hospital mortality risk in critically ill coronary artery disease patients.¹⁸ In addition, research has found a substantial connection

between ePWV and higher in-hospital mortality risk in critically ill patients with acute kidney injury, with ePWV functioning as an independent predictor of in-hospital mortality.¹⁹ Similar findings have been reported in critically ill patients with chronic kidney disease and associated atherosclerotic heart disease, in which ePWV appears to be a possible marker for measuring in-hospital and one-year mortality, with its elevation closely linked to increased mortality risk.²⁰ The present data also show a substantial positive relationship between ePWV and 28-day mortality risk in patients with sepsis, further highlighting the prognostic value of ePWV in critical illnesses. Notably, a recent study by Liu et al.¹² based on the same database also corroborated the prognostic value of ePWV, thereby supporting the accuracy of the present findings. However, while they identified a nonlinear (U-shaped) relationship between ePWV and 30-day mortality risk, the present study's analysis employing RCS revealed a linear positive association between ePWV and 28-day mortality. This discrepancy in conclusions may be attributable to differences in outcome definitions and patient selection strategies, further underscoring the scientific necessity of independently validating the predictive characteristics of ePWV. Of note, ePWV is a key prognostic biomarker rather than a direct therapeutic intervention. Its primary value lies in enabling early identification of high-risk patients, facilitating precise

Fig. 4. Performance evaluation and decision curve analysis of 28-day mortality prediction models.



(A) Receiver operating characteristic curve comparing discriminative ability of the ePWV-only model, ePWV-adjusted model, and combined model. (B) Decision curve analysis evaluating net clinical benefit across threshold probabilities for different models.

AUC: area under the curve; ePWV: estimated pulse wave velocity

Note: The ePWV-adjusted model included covariates from the final association analysis model; the combined model included predictors selected by LASSO.

risk stratification and guiding individualised treatment strategies and management optimisation. Future research should explore the potential of ePWV for risk prediction in other critical illnesses, with the goal of integrating it into clinical decision-making to improve patient outcomes.

The processes driving the rise in ePWV in sepsis are not well understood and may include 3 components. Patients with sepsis have elevated levels of inflammatory mediators, including TNF- α and IL-1 β ,²¹ which can cause endothelial dysfunction and thrombosis.²² This may lead to an increase in ePWV. Furthermore, during sepsis, levels of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol decrease, while oxidation of low-density lipoprotein cholesterol increases, increasing the risk of cellular apoptosis and atherosclerosis.²³ This may also increase ePWV. Finally, patients with sepsis often have hypotension, which can cause reduced tissue perfusion pressure²⁴ and hypoxia-induced vascular smooth muscle cell proliferation and migration, both of which contribute to atherosclerosis.²⁵ Several studies have found a link between chronic hypoxic conditions (e.g. chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome) and an increase in PWV.^{26,27}

Furthermore, the present study's subgroup analysis reported that invasive ventilation and the absence of malignant tumours increase the risk of 28-day mortality in patients with sepsis. The need for invasive ventilation is a factor associated with higher mortality in patients with sepsis.²⁸ Patients with sepsis who require invasive ventilation have much higher mortality rates (41.33% vs 8.91%).²⁹ This may be because invasive ventilation can cause ventilator-associated pneumonia,³⁰ which worsens the course of sepsis. Invasive ventilation might cause haemodynamic instability after intubation,^{31,32} which may worsen the prognosis for patients with sepsis who already have circulatory dysfunction.³³ The greater mortality risk among patients without malignant tumours may be related to different treatment strategies or monitoring intensity received by patients with malignancy, though these hypotheses require further validation.

Notably, the subgroup analysis revealed variation in the association between ePWV and 28-day mortality across racial groups. Among White patients, ePWV was significantly positively associated with mortality risk; no significant association was observed in Black patients. Several factors may explain this finding. First, the relatively small sample size of the Black subgroup may have limited the statistical power to detect a significant association. Second, prior evidence indicates racial differences in arterial stiffness; for instance, one study found that Black boys had significantly higher carotid-radial, carotid-femoral, and carotid-dorsal foot PWVs, along with greater carotid intima-media thickness, than their White counterparts,³⁴

indicating that Black individuals may have inherently higher baseline arterial stiffness, which could influence the predictive value of ePWV in this population. Additionally, racial differences in socioeconomic factors, healthcare access, dietary intake, and comorbidity distribution may have confounded the results.^{35,36} Therefore, these racial subgroup findings, particularly the null result in Black patients, should be interpreted with caution. Future prospective studies across diverse racial populations, including Asian and African cohorts, are needed to validate the generalisability of ePWV's predictive value and explore the possibility of race-specific thresholds.

While this study has several strengths, some limitations exist. First, because this was a retrospective study, recall and information bias could not be avoided. Despite adjusting for confounding variables as much as possible, there may still be confounding factors affecting the association between ePWV and mortality, such as lifestyle factors and genetic susceptibility. Second, the authors investigated only the association of ePWV with in-hospital mortality in patients with sepsis. Whether changes in ePWV have long-term effects on patients with sepsis should be investigated, and prospective cohort studies could enable more precise temporal tracking of the impact of ePWV on septic mortality and prognosis. Third, this study included only patients with sepsis admitted to the ICU, which may influence patients' haemodynamic status. Future research that directly measures ePWV under stable conditions, could provide a more accurate and comprehensive understanding of the relationship between ePWV and septic patient mortality. Finally, the data in MIMIC primarily comprise patients from a single geographic region, limiting the generalisability of results to other populations, and the associations identified in this study need further validation in different populations.

CONCLUSION

The results identify ePWV as an independent mortality predictor in sepsis. Future external validation studies across diverse racial and geographic populations are urgently needed to confirm the generalisability and robustness of ePWV and provide stronger evidence supporting its use as a clinical risk stratification tool.

Supplementary materials

Fig. S1. Variable selection using Cox-LASSO regression.

Table S1. Number and proportion of missing variables.

Table S2. Variance inflation factor of variables for multivariate Cox regression.

Ethics statement

The data used in this study were obtained from the publicly available MIMIC-IV database. Ethical

approval and consent were not required for this study in accordance with national guidelines.

Declarations

The authors declare they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. This paper was supported by the Hainan Provincial Natural Science Foundation High-Level Talents Program (823RC571), Hainan Provincial Natural Science Foundation of China (824QN374), and NHC Key Laboratory of Tropical Disease Control, Hainan Medical University (2023NHCTDCKFKT11002). There is no conflict of interest to declare.

REFERENCES

- Kim MH, Choi JH. An Update on Sepsis Biomarkers. *Infect Chemother* 2020;52:1-18.
- Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200-11.
- Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. *SAGE Open Med* 2019;7:2050312119835043.
- Imran BMN. Sepsis and cardiovascular events: The story so far. *Ann Acad Med Singap* 2022;51:261-2.
- Gusev E, Sarapultsev A. Atherosclerosis and Inflammation: Insights from the Theory of General Pathological Processes. *Int J Mol Sci* 2023;24:7910.
- Xuereb RA, Magri CJ, Xuereb RG. Arterial Stiffness and its Impact on Cardiovascular Health. *Curr Cardiol Rep* 2023;25:1337-49.
- Kazune S, Grabovskis A, Cescon C, et al. Association between increased arterial stiffness and clinical outcomes in patients with early sepsis: a prospective observational cohort study. *Intensive Care Med Exp* 2019;7:26.
- Xu M, Wang W, Chen R, et al. Individual and combined associations of estimated pulse wave velocity and systemic inflammation response index with risk of stroke in middle-aged and older Chinese adults: a prospective cohort study. *Front Cardiovasc Med* 2023;10:1158098.
- Heffernan KS, Wilmoth JM, London AS. Estimated Pulse Wave Velocity and All-Cause Mortality: Findings From the Health and Retirement Study. *Innov Aging* 2022;6:igac056.
- Hametner B, Wassertheurer S, Mayer CC, et al. Aortic Pulse Wave Velocity Predicts Cardiovascular Events and Mortality in Patients Undergoing Coronary Angiography: A Comparison of Invasive Measurements and Noninvasive Estimates. *Hypertension* 2021;77:571-81.
- Greve SV, Blicher MK, Kruger R, et al. Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity. *J Hypertens* 2016;34:1279-89.
- Liu S, Zhang M, Ye W, et al. Association between estimated pulse wave velocity and the risk of mortality in patients with sepsis patients: A cohort study. *Sci Prog* 2026;109:368504251414251.
- Chen L, Lu H, Lv C, et al. Association between red blood cells transfusion and 28-day mortality rate in septic patients with concomitant chronic kidney disease. *Sci Rep* 2024;14:23769.
- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
- Ji C, Wang G, Huang Z, et al. Estimated pulse wave velocity and risk of new-onset heart failure. *ESC Heart Fail* 2024;11:2120-8.
- Guo Q, Qu P, Cui W, et al. Organism type of infection is associated with prognosis in sepsis: an analysis from the MIMIC-IV database. *BMC Infect Dis* 2023;23:431.
- Wang C, Zheng J, Wang J, et al. Cox-LASSO Analysis for Hospital Mortality in Patients With Sepsis Received Continuous Renal Replacement Therapy: A MIMIC-III Database Study. *Front Med (Lausanne)* 2022;8:778536.
- Gu Y, Han X, Liu J, et al. Prognostic significance of the estimated pulse wave velocity in critically ill patients with coronary heart disease: analysis from the Medical Information Mart for Intensive Care IV database. *Eur Heart J Qual Care Clin Outcomes* 2025;11:739-46.
- Cui X, Hu Y, Li D, et al. Association between estimated pulse wave velocity and in-hospital mortality of patients with acute kidney injury: a retrospective cohort analysis of the MIMIC-IV database. *Ren Fail* 2024;46:2313172.
- Cui X, Shi H, Hu Y, et al. Association between estimated pulse wave velocity and in-hospital and one-year mortality of patients with chronic kidney disease and atherosclerotic heart disease: a retrospective cohort analysis of the MIMIC-IV database. *Ren Fail* 2024;46:2387932.
- Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol* 2017;39:517-28.
- Theofilis P, Sagris M, Oikonomou E, et al. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines* 2021;9:781.
- Laudanski K. Persistence of Lipoproteins and Cholesterol Alterations after Sepsis: Implication for Atherosclerosis Progression. *Int J Mol Sci* 2021;22:10517.
- Srzic I, Nesek Adam V, Tunjić Pejak D. Sepsis Definition: What's New in the Treatment Guidelines. *Acta Clin Croat* 2022;61:67-72.
- Jain T, Nikolopoulou EA, Xu Q, et al. Hypoxia inducible factor as a therapeutic target for atherosclerosis. *Pharmacol Ther* 2018;183:22-33.
- Crim C, Anderson JA, Calverley PMA, et al. Pulse Wave Velocity in Chronic Obstructive Pulmonary Disease and the Impact of Inhaled Therapy (SUMMIT): A Randomized Double-Blind Clinical Trial. *Am J Respir Crit Care Med* 2020;201:1307-10.
- Wang J, Yu W, Gao M, et al. Impact of Obstructive Sleep Apnea Syndrome on Endothelial Function, Arterial Stiffening, and Serum Inflammatory Markers: An Updated Meta-analysis and Metaregression of 18 Studies. *J Am Heart Assoc* 2015;4:e002454.
- Mohamed AKS, Mehta AA, James P. Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. *Lung India* 2017;34:330-5.
- Dhital R, Basnet S, Poudel DR. Predictors and outcome of invasive mechanical ventilation in hospitalized patients with sepsis: data from National Inpatient Sample. *J Community Hosp Intern Med Perspect* 2018;8:49-52.
- Mumtaz H, Saqib M, Khan W, et al. Ventilator associated pneumonia in intensive care unit patients: a systematic review. *Ann Med Surg (Lond)* 2023;85:2932-9.
- Morris IS, Bassi T, Oosthuysen C, et al. Phrenic Nerve Stimulation for Acute Respiratory Failure. *Respir Care* 2023;68:1736-47.
- Al-Saadi MA, Heidari B, Donahue KR, et al. Pre-Existing Right Ventricular Dysfunction as an Independent Risk Factor for

- Post Intubation Cardiac Arrest and Hemodynamic Instability in Critically Ill Patients: A Retrospective Observational Study. *J Intensive Care Med* 2023;38:169-78.
33. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev* 2016;274:330-53.
34. Mokwatsi GG, Schutte AE, Kruger R. Ethnic differences regarding arterial stiffness of 6-8-year-old black and white boys. *J Hypertens* 2017;35:960-7.
35. Mels CM, Delles C, Louw R, et al. Central systolic pressure and a nonessential amino acid metabolomics profile: the African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension. *J Hypertens* 2019;37:1157-66.
36. Luk AOY, Fan Y, Fan B, et al. Heterogeneity in the development of diabetes-related complications: narrative review of the roles of ancestry and geographical determinants. *Diabetologia* 2025;68:2386-404.