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Association between blood glucose level trajectories and 30-day mortality risk in patients with acute ischemic stroke: analysis of the MIMIC database 2001–2019

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Abstract

Background Hyperglycemia is one of the most common comorbidities in patients with acute ischemic stroke (AIS). This study aimed to assess the impact of short-term longitudinal blood glucose level change trajectories on the 30-day mortality risk in patients with AIS.

Methods Data for AIS patients were obtained from the 2001–2019 Medical Information Mart for Intensive Care (MIMIC) database. The latent growth mixture modeling (LGMM) was utilized to classify a patient's blood glucose level trajectory within 24 h of admission. Cox regression analyses were applied to examine the relationship between blood glucose levels at admission and blood glucose level trajectories and the risk of 30-day mortality in patients with AIS.

Results A total of 2,432 patients with AIS were included in this retrospective cohort study, with 30-day mortality occurring in 574 (23.60%) patients. The median glucose levels of all patients were 136.00 (110.00, 178.00) mg/dL. Four blood glucose level trajectories were identified: low level-stable trend (type 1), moderate level-stable trend (type 2), high level-decreasing-increasing trend (type 3), and moderate level-increasing-decreasing trend (type 4). Type 2 blood glucose level trajectory was associated with an increased risk of 30-day mortality compared with type 1 blood glucose level trajectory [hazard ratio (HR) = 1.28, 95% confidence interval (CI): 1.03–1.59), but there were no significant associations between type 3 (HR = 1.16, 95%CI: 0.77–1.74) and type 4 (HR = 1.44, 95%CI: 0.84–2.45) trajectories and 30-day mortality risk. Subgroup analysis demonstrated that the association between type 2 trajectory and 30-day mortality risk was observed in patients aged ≥ 65 years (HR = 1.37, 95%CI: 1.05–1.79), female (HR = 1.42, 95%CI: 1.05–1.94), with (HR = 1.44, 95%CI: 1.02–2.02) or without (HR = 1.42, 95%CI: 1.01–1.99) diabetes, and not using insulin (HR = 2.80, 95%CI: 1.43–5.49).

Conclusion AIS patients with consistently high blood glucose levels within 24 h of admission increased the risk of 30-day mortality.

Keywords Acute ischemic stroke, Blood glucose, Trajectory, 30-day mortality

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Background

Acute ischemic stroke (AIS) is an acute condition in which brain cells are damaged due to reduced blood flow to the brain [1]. AIS is one of the major types of stroke, which causes a significant disease burden and is a leading cause of death and disability [2]. Stroke is the second leading cause of death globally, with nearly 7 million stroke-related deaths, more than 100 million stroke patients and 12 million new stroke cases worldwide in 2019 [3]. Major risk factors for the development of AIS include high blood pressure, high cholesterol, cigarette smoking, diabetes, and obesity [4].

Hyperglycemia is one of the most common comorbidities in patients with AIS [5, 6]. Hyperglycemia promotes thrombotic inflammation through activation of endothelial cells, platelets, and neutrophils, and is associated with a poor short-term prognosis of hemorrhagic transformation, deterioration of neurological function, and death in patients with AIS [7–9]. Some studies suggest that changes in blood glucose levels may be more valuable for clinical monitoring than baseline blood glucose levels [10–12]. Blood glucose level trajectory refers to the longitudinal change in an individual's blood glucose over time, which better reflects blood glucose levels, the range and direction of blood glucose changes at different time points than variability indicators [10, 11]. Li et al. showed that individuals with longitudinally elevated fasting glucose level trajectories had a higher risk of death even if they had normal glucose levels at baseline [12]. The longitudinal trajectory of common indicators (e.g., hemoglobin, etc.) over time was also significantly associated with short-term prognosis in critically ill patients [13, 14]. However, the impact of the longitudinal trajectory of short-term glucose changes on the prognosis of patients with AIS remains unclear. Therefore, this study intended to investigate the association between different short-term longitudinal blood glucose level change trajectories and the 30-day mortality risk in patients with AIS, to provide a basis for glucose management in patients with AIS.

Methods

Population and study design

Data for this retrospective cohort study were obtained from the Medical Information Mart for Intensive Care (MIMIC) database from 2001 to 2019. MIMIC is a large, single-center database of de-identified hospitalization-related information for patients admitted to the intensive care unit (ICU) at Beth Israel Deaconess Medical Center [15, 16]. MIMIC database contains patient demographics, laboratory test results, vital sign measurements, procedures, medications, medical history, and mortality data. The inclusion criteria for patients were as follows: (1) patients aged ≥ 18 years old; (2) patients already diagnosed with AIS on ICU admission; (3) patients hospitalized in an ICU for at least 24 h; and (4) patients with repeated glucose measurements (≥ 2) within 24 h of ICU admission. Patients with missing survival information were excluded. AIS was determined from the International Classification of Diseases, ninth/tenth revision (ICD-9/10) codes [ICD-9: 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491; ICD-10: I63xxx) in the MIMIC database. For patients with multiple hospitalization records, data were collected only for the patient's first ICU admission. The requirement of ethical approval for this was waived by the Institutional Review Board of Shanxi Provincial People's Hospital, because the data was accessed from MIMIC database (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Shanxi Provincial People's Hospital due to retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Outcome

The outcome of this study was 30-day mortality, which occurred within 30 days of the patient's admission to the ICU. The follow-up period was from the time the patient was admitted to the ICU to the subsequent 30 days or mortality during this period.

Exposure

The exposures in this study were blood glucose levels at ICU admission and the blood glucose level trajectories within 24 h of ICU admission. Current stroke management guidelines categorized patients' blood glucose levels into 3 groups: normoglycemia (< 140 mg/dL), moderate hyperglycemia (140–180 mg/dL), and severe hyperglycemia (≥ 180 mg/dL) [17]. Therefore, when blood glucose levels were analyzed as a categorical variable, the blood glucose levels in this study were classified into 3 categories (< 140 mg/dL, 140–180 mg/dL, and ≥ 180 mg/dL). The latent growth mixture modeling (LGMM) was utilized to classify blood glucose level trajectories. The LGMM assumes that the population consists of multiple potential categories, each with similar trajectories and characteristics [18]. A key factor in generating LGMM is determining the number of potential categories. The number of suitable LGMM categories should satisfy that the Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC) are as small as possible [19], the Entropy needs to be greater than 0.7, the minimum share of each category should not be less than 1%, and the average value of the posterior probability in each category needs to be greater than 70%. After screening, 4 categories of blood glucose level trajectories were the most suitable in this study (Supplement Tables 1 and 2).

Table 1 Characteristics of acute ischemic stroke (AIS) patients with different blood glucose level trajectories

Variables	Total (*N* = 2432)	Blood glucose level trajectories				*P*
		Type 1 (*N* = 1946)	Type 2 (*N* = 365)	Type 3 (*N* = 76)	Type 4 (*N* = 45)	
Age, years, Mean (± SD)	66.96 (± 15.79)	67.26 (± 16.15)	65.08 (± 14.22)	68.67 (± 14.09)	66.63 (± 14.09)	0.048
Gender, n (%)						0.015
Female	1209 (49.71)	975 (50.10)	174 (47.67)	46 (60.53)	14 (31.11)	
Male	1223 (50.29)	971 (49.90)	191 (52.33)	30 (39.47)	31 (68.89)	
Race, n (%)						0.806
White	1541 (63.36)	1243 (63.87)	220 (60.27)	48 (63.16)	30 (66.67)	
Black	243 (9.99)	186 (9.56)	44 (12.05)	8 (10.53)	5 (11.11)	
Other	250 (10.28)	204 (10.48)	33 (9.04)	9 (11.84)	4 (8.89)	
Unknown	398 (16.37)	313 (16.08)	68 (18.63)	11 (14.47)	6 (13.33)	
Admission type, n (%)						< 0.001
Neuro ICU	309 (12.71)	266 (13.67)	35 (9.59)	5 (6.58)	3 (6.67)	
Cardiac ICU	584 (24.01)	466 (23.95)	91 (24.93)	22 (28.95)	5 (11.11)	
SICU	1039 (42.72)	867 (44.55)	134 (36.71)	22 (28.95)	16 (35.56)	
Other	500 (20.56)	347 (17.83)	105 (28.77)	27 (35.53)	21 (46.67)	
Heart rate, bpm, Mean (± SD)	85.70 (± 19.86)	84.41 (± 19.38)	91.06 (± 20.54)	94.92 (± 22.27)	82.42 (± 19.64)	< 0.001
Systolic, mmHg, Mean (± SD)	134.23 (± 28.43)	134.49 (± 28.07)	134.45 (± 30.16)	126.84 (± 24.55)	133.92 (± 34.18)	0.077
Diastolic, mmHg, Mean (± SD)	71.09 (± 18.73)	70.99 (± 18.32)	72.72 (± 20.76)	65.68 (± 18.75)	71.62 (± 17.17)	0.039
MAP, mmHg, Mean (± SD)	92.14 (± 19.21)	92.15 (± 18.78)	93.30 (± 21.24)	86.07 (± 18.47)	92.39 (± 20.05)	0.030
Respiratory rate, insp/min, Mean (± SD)	19.02 (± 6.01)	18.60 (± 5.74)	20.89 (± 6.98)	20.26 (± 6.07)	20.07 (± 5.74)	< 0.001
Temperature, Deg.C, Mean (± SD)	36.67 (± 0.95)	36.65 (± 0.89)	36.74 (± 1.09)	36.75 (± 1.52)	36.81 (± 0.67)	0.249
Sepsis, n (%)						< 0.001
No	2067 (84.99)	1689 (86.79)	283 (77.53)	62 (81.58)	33 (73.33)	
Yes	365 (15.01)	257 (13.21)	82 (22.47)	14 (18.42)	12 (26.67)	
Cardiogenic shock, n (%)						< 0.001
No	2314 (95.15)	1871 (96.15)	333 (91.23)	69 (90.79)	41 (91.11)	
Yes	118 (4.85)	75 (3.85)	32 (8.77)	7 (9.21)	4 (8.89)	
Diabetes, n (%)						< 0.001
No	1626 (66.86)	1460 (75.03)	124 (33.97)	25 (32.89)	17 (37.78)	
Yes	806 (33.14)	486 (24.97)	241 (66.03)	51 (67.11)	28 (62.22)	
Anemia, n (%)						0.709
No	773 (31.78)	622 (31.96)	115 (31.51)	20 (26.32)	16 (35.56)	
Yes	1659 (68.22)	1324 (68.04)	250 (68.49)	56 (73.68)	29 (64.44)	
Atrial fibrillation, n (%)						0.085
No	1524 (62.66)	1195 (61.41)	246 (67.40)	52 (68.42)	31 (68.89)	
Yes	908 (37.34)	751 (38.59)	119 (32.60)	24 (31.58)	14 (31.11)	
SAPSII, Mean (± SD)	38.69 (± 13.82)	37.26 (± 13.12)	43.54 (± 14.71)	46.92 (± 16.51)	47.53 (± 14.27)	< 0.001
SOFA, Mean (± SD)	5.67 (± 3.74)	5.25 (± 3.47)	7.28 (± 4.21)	7.04 (± 4.66)	8.38 (± 4.28)	< 0.001
GCS, n (%)						0.510
<13	1017 (41.82)	802 (41.21)	164 (44.93)	34 (44.74)	17 (37.78)	
≥13	1415 (58.18)	1144 (58.79)	201 (55.07)	42 (55.26)	28 (62.22)	
CCI, Mean (± SD)	5.06 (± 2.67)	4.97 (± 2.71)	5.25 (± 2.41)	5.99 (± 2.59)	5.69 (± 2.56)	0.001
SPO2, %, M (Q_1, Q_3)	99.00 (96.00, 100.00)	99.00 (96.00, 100.00)	99.00 (96.00, 100.00)	99.00 (95.00, 100.00)	97.00 (94.00, 99.00)	< 0.001
WBC, K/uL, M (Q_1, Q_3)	11.50 (8.30, 15.10)	11.20 (8.20, 14.60)	13.00 (9.50, 17.30)	12.05 (9.78, 16.77)	12.60 (8.50, 19.10)	< 0.001
Platelet, K/uL, M (Q_1, Q_3)	203.00 (148.00, 269.00)	201.00 (148.25, 264.00)	209.00 (139.00, 286.00)	209.50 (163.00, 260.50)	220.00 (160.00, 280.00)	0.554
Hemoglobin, g/dL, Mean (± SD)	11.20 (± 2.35)	11.19 (± 2.34)	11.35 (± 2.35)	10.47 (± 2.66)	11.77 (± 2.40)	0.010
RDW, %, Mean (± SD)	14.73 (± 2.10)	14.75 (± 2.14)	14.61 (± 1.84)	14.94 (± 2.34)	14.75 (± 1.89)	0.540
Hematocrit, %, Mean (± SD)	33.68 (± 6.84)	33.61 (± 6.77)	34.27 (± 6.91)	31.82 (± 7.91)	35.16 (± 6.72)	0.014
Blood creatinine, mg/dL, M (Q_1, Q_3)	1.00 (0.70, 1.40)	0.90 (0.70, 1.30)	1.10 (0.80, 1.50)	1.30 (0.90, 1.92)	1.40 (1.10, 2.40)	< 0.001
BUN, mg/dL, Mean (± SD)	24.82 (± 19.17)	23.66 (± 18.32)	27.35 (± 19.25)	33.42 (± 22.39)	40.02 (± 32.82)	< 0.001
Magnesium, mg/dL, M (Q_1, Q_3)	1.90 (1.70, 2.20)	1.90 (1.70, 2.20)	1.90 (1.60, 2.10)	1.90 (1.70, 2.02)	1.90 (1.80, 2.10)	< 0.001

Table 1 (continued)

Variables	Total (*N* = 2432)	Blood glucose level trajectories				*P*
		Type 1 (*N* = 1946)	Type 2 (*N* = 365)	Type 3 (*N* = 76)	Type 4 (*N* = 45)	
INR, M (Q_1, Q_3)	1.20 (1.10, 1.40)	1.20 (1.10, 1.40)	1.20 (1.10, 1.50)	1.30 (1.12, 1.72)	1.30 (1.20, 1.40)	0.024
PT, sec, M (Q_1, Q_3)	13.70 (12.40, 15.70)	13.70 (12.40, 15.60)	13.80 (12.50, 16.20)	14.29 (12.57, 17.98)	14.20 (12.70, 15.40)	0.108
Anion gap, mEq/L, Mean (± SD)	14.94 (± 4.10)	14.38 (± 3.70)	17.04 (± 4.79)	17.62 (± 5.15)	17.58 (± 3.99)	< 0.001
Urine output, mL, M (Q_1, Q_3)	1578.50 (999.75, 2380.00)	1590.00 (1050.00, 2380.00)	1580.00 (830.00, 2405.00)	1144.50 (671.75, 2197.50)	1570.00 (845.00, 2425.00)	0.005
Ventilation, n (%)						< 0.001
No	654 (26.89)	556 (28.57)	67 (18.36)	26 (34.21)	5 (11.11)	
Yes	1778 (73.11)	1390 (71.43)	298 (81.64)	50 (65.79)	40 (88.89)	
Vasopressor, n (%)						< 0.001
No	1337 (54.98)	1117 (57.40)	168 (46.03)	39 (51.32)	13 (28.89)	
Yes	1095 (45.02)	829 (42.60)	197 (53.97)	37 (48.68)	32 (71.11)	
Anticoagulants, n (%)						0.004
No	1158 (47.62)	952 (48.92)	149 (40.82)	42 (55.26)	15 (33.33)	
Yes	1274 (52.38)	994 (51.08)	216 (59.18)	34 (44.74)	30 (66.67)	
Antiplatelet agents, n (%)						0.018
No	2431 (99.96)	1946 (100.00)	365 (100.00)	76 (100.00)	44 (97.78)	
Yes	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.22)	
Statins, n (%)						0.235
No	1143 (47.00)	913 (46.92)	164 (44.93)	39 (51.32)	27 (60.00)	
Yes	1289 (53.00)	1033 (53.08)	201 (55.07)	37 (48.68)	18 (40.00)	
Insulin, n (%)						< 0.001
No	446 (18.34)	406 (20.86)	29 (7.95)	8 (10.53)	3 (6.67)	
Yes	1986 (81.66)	1540 (79.14)	336 (92.05)	68 (89.47)	42 (93.33)	
Thrombectomy, n (%)						0.146
No	2378 (97.78)	1907 (98.00)	351 (96.16)	75 (98.68)	45 (100.00)	
Yes	54 (2.22)	39 (2.00)	14 (3.84)	1 (1.32)	0 (0.00)	
Thrombolysis, n (%)						0.488
No	2307 (94.86)	1841 (94.60)	348 (95.34)	75 (98.68)	43 (95.56)	
Yes	125 (5.14)	105 (5.40)	17 (4.66)	1 (1.32)	2 (4.44)	
Glucose, mg/dL, M (Q_1, Q_3)	136.00 (110.00, 178.00)	126.50 (106.00, 150.00)	232.00 (188.00, 280.00)	355.50 (300.00, 476.00)	212.00 (161.00, 355.00)	< 0.001
Glucose, mg/dL, n (%)						< 0.001
<140	1294 (53.21)	1251 (64.29)	30 (8.22)	4 (5.26)	9 (20.00)	
140–200	715 (29.40)	614 (31.55)	89 (24.38)	1 (1.32)	11 (24.44)	
≥200	423 (17.39)	81 (4.16)	246 (67.40)	71 (93.42)	25 (55.56)	
Status, n (%)						< 0.001
Survival or Censored	1858 (76.40)	1531 (78.67)	247 (67.67)	50 (65.79)	30 (66.67)	
Dead	574 (23.60)	415 (21.33)	118 (32.33)	26 (34.21)	15 (33.33)	

Note: type 1, low level-stable trend; type 2, moderate level-stable trend; type 3, high level-decreasing-increasing trend; type 4, moderate level-increasing-decreasing trend; ICU, intensive care unit; SICU, surgical ICU; MAP, mean arterial pressure; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow coma scale; CCI, Charlson comorbidity index; SPO2, oxyhemoglobin saturation; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; INR, international normalized ratio; PT: prothrombin time

Covariates

The selection of covariates was based primarily on previous studies of ischemic stroke patients admitted to the ICU [20, 21]. Patient characteristics were collected including age, gender (female, male), race (White, Black, other, unknown), admission type (neuro ICU, cardiac ICU, surgical ICU, others), heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate, temperature, sepsis (no, yes), cardiogenic shock (no, yes), diabetes (no, yes), anemia (no, yes), atrial fibrillation (no, yes), Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS) (<15, ≥15), Charlson comorbidity index (CCI), oxyhemoglobin saturation (SPO_2), white blood cells (WBC), platelet, hemoglobin, red blood cell distribution width (RDW), hematocrit, blood creatinine, blood urea nitrogen (BUN), magnesium levels, international normalized ration (INR),

Table 2 The associations of blood glucose levels and blood glucose level trajectories with the risk of 30-day mortality in patients with acute ischemic stroke (AIS)

Variables	Outcome/Total	Unadjusted model		Model 1	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Glucose levels	*N* = 574/2432	1.13 (1.05–1.20)	< 0.001	1.07 (0.99–1.14)	0.075
Glucose levels					
<140 mg/dL	*N* = 259/1294	Ref		Ref	
140–180 mg/dL	*N* = 129/549	1.11 (0.90–1.37)	0.322	0.99 (0.80–1.23)	0.940
≥180 mg/dL	*N* = 186/589	1.42 (1.17–1.71)	< 0.001	1.31 (1.08–1.60)	0.007
Blood glucose level trajectories					
Type 1	*N* = 415/1946	Ref		Ref	
Type 2	*N* = 118/365	1.37 (1.12–1.68)	0.002	1.28 (1.03–1.59)	0.028
Type 3	*N* = 26/76	1.47 (0.99–2.19)	0.055	1.16 (0.77–1.74)	0.482
Type 4	*N* = 15/45	1.67 (1.00-2.79)	0.052	1.44 (0.84–2.45)	0.183

Note: type 1, low level-stable trend; type 2, moderate level-stable trend; type 3, high level-decreasing-increasing trend; type 4, moderate level-increasing-decreasing trend; HR, hazard ratio; CI, confidence interval;

Model 1 was multivariable Cox regression analysis adjusted for age, gender, race, admission type, respiratory rate, temperature, SOFA, GCS, CCI, platelet, anemia, RDW, BUN, anion gap, urine output, anticoagulants, statins, thrombectomy, atrial fibrillation, and thrombolysis

prothrombin time (PT), anion gap, urine output, ventilation (no, yes), vasopressor (no, yes), anticoagulants (no, yes), antiplatelet agents (no, yes), statins (no, yes), insulin (no, yes), thrombectomy (no, yes), and thrombolysis (no, yes). Urine output was defined as the sum of urinary output within 24 h of admission to the ICU.

Statistical analysis

Skewness and kurtosis methods were used to assess the normality of continuous variables. Continuous variables were described as the mean ± standard deviation (SD) or median and quartile [M (Q1, Q3)], and categorical variables were described as numbers and percentages [n (%)]. The ANOVA or Welch ANOVA test or Kruskal-Wallis H test was used for comparison between groups of continuous variables, and the Chi-square test or Fisher's exact test was used for comparison between groups of categorical variables. Variables with more than 10% of missing values were excluded (Supplement Table 3), and missing values for the remaining variables were imputed using the multiple imputation method (Supplement Table 4).

Univariable Cox regression analysis was applied to screen for confounders related to 30-day mortality, and variables with $P<0.1$ were adjusted in multivariable Cox regression analysis. After screening, multivariable Cox regression analysis adjusted for age, gender, race, admission type, respiratory rate, temperature, SOFA, CCI, platelet, anemia, RDW, BUN, anion gap, urine output, anticoagulants, statins, thrombectomy, atrial fibrillation, and thrombolysis (Supplement Table 5). Because of the important effect of anemia and thrombolysis on AIS [21, 22], anemia and thrombolysis were adjusted in the multivariable model in addition to variables with $P<0.1$. Univariable and multivariable Cox regression analyses were applied to examine the relationship between blood glucose levels at ICU admission and blood glucose level trajectories and the risk of 30-day mortality in patients with AIS. Hazard ratio (HR) and 95% confidence interval (CI) were used to report relationships. Subgroup analysis was performed based on age (<65, ≥65 years), gender (female, male), diabetes (no, yes), and insulin use (no, yes). Statistical analyses were performed using R 4.2.3 software (Institute for Statistics and Mathematics, Vienna, Austria), and $P<0.05$ was considered statistically significant.

Results

Characteristics of patients

A total of 4,705 patients diagnosed with AIS were recorded in the MIMIC database between 2001 and 2019. After screening, 2,273 patients were excluded and 2,432 eligible patients were included in this study (Fig. 1). There were differences in characteristics between included and excluded patients (Supplement Table 6). The characteristics of patients with different blood glucose level trajectories were presented in Table 1. Among these 2,432 patients, 30-day mortality occurred in 574 (23.60%) patients. The mean age (SD) was 66.96 (±15.79) years and 1,209 (49.71%) patients were female. The median blood glucose levels were 136.00 (110.00, 178.00) mg/dL. There were 1,946 (80.02%) patients with type 1 blood glucose level trajectory (low level-stable trend), 365 (15.00%) patients with type 2 blood glucose level trajectory (moderate level-stable trend), 76 (3.13%) patients with type 3 blood glucose level trajectory (high level-decreasing-increasing trend), and 45 (1.85%) patients with type 4 blood glucose level trajectory (moderate level-increasing-decreasing trend). The blood glucose level trajectories for these four types were shown in Fig. 2.

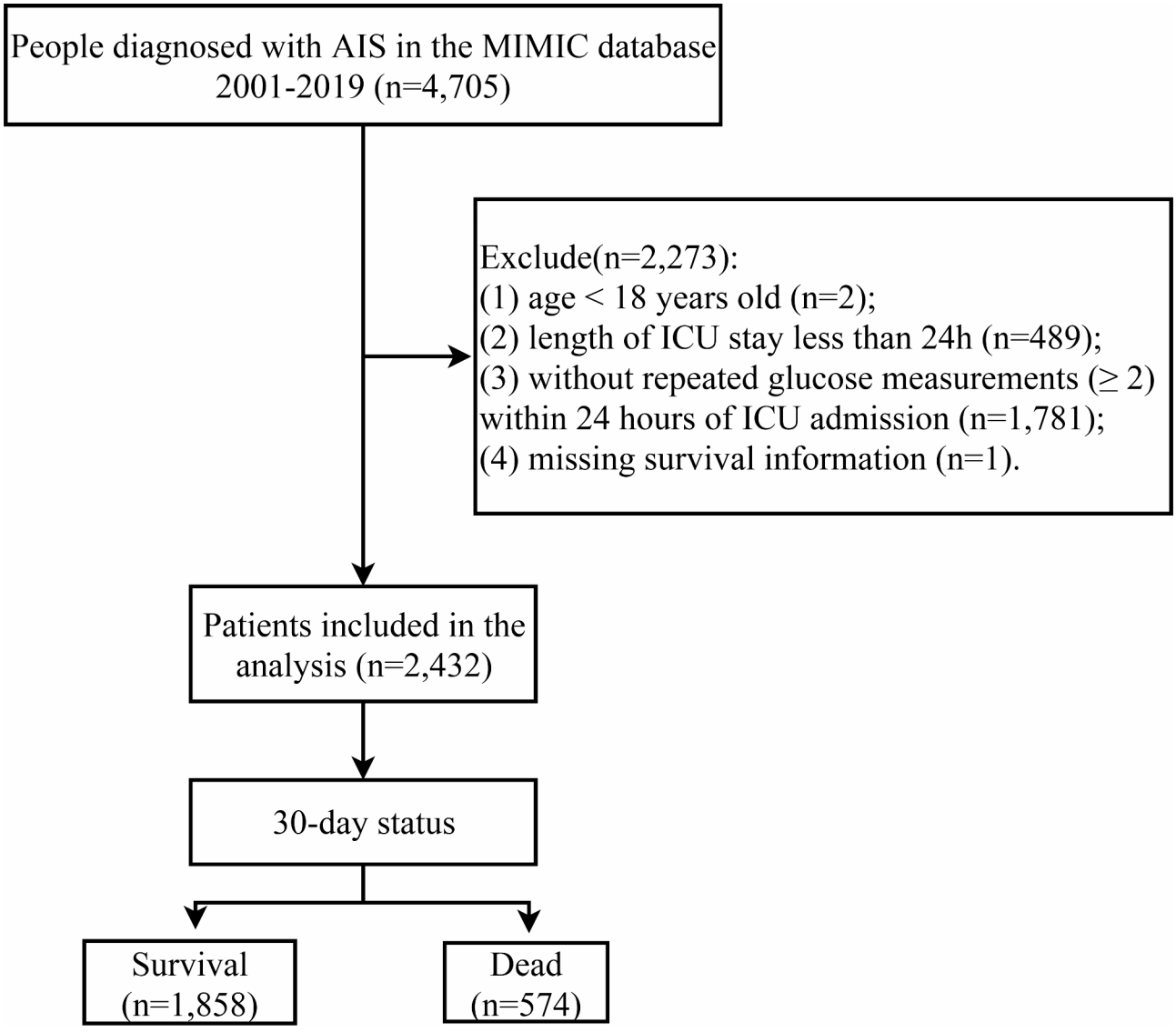

Fig. 1 Screening flowchart for the study population

Association between blood glucose levels and blood glucose level trajectories and 30-day mortality in patients with AIS

The associations of blood glucose levels and blood glucose level trajectories with the risk of 30-day mortality in patients with AIS were presented in Table 2. High blood glucose levels were associated with an increased risk of 30-day mortality in the univariable analysis (HR=1.13, 95%CI: 1.05–1.20), but not in the multivariable analysis (HR=1.07, 95%CI: 0.99–1.14). When glucose levels were analyzed as a categorical variable, blood glucose levels≥180 mg/dL (HR=1.31, 95%CI: 1.08–1.60) were linked to a higher risk of 30-day mortality compared with glucose levels of <140 mg/dL, but not in blood glucose levels of 140–180 mg/dL (HR=0.99, 95%CI: 0.80–1.23). The association between blood glucose levels at ICU admission and 30-day mortality risk in different subgroups of the population was presented in Supplement Table 7. Blood glucose levels of ≥180 mg/dL in patients aged<65 years (HR=1.77, 95%CI: 1.22–2.56), with (HR=1.73, 95%CI: 1.20–2.50) or without (HR=1.34, 95%CI: 1.01–1.77) diabetes, and using insulin (HR=1.24, 95%CI: 1.01–1.55) were associated with a higher risk of 30-day mortality.

For blood glucose level trajectories, type 2 blood glucose level trajectory was related to a higher risk of 30-day mortality compared with type 1 trajectory in both univariable analysis (HR=1.37, 95%CI: 1.12–1.68) and multivariable analysis (HR=1.28, 95%CI: 1.03–1.59), but no significant associations were found in type 3 (HR=1.16, 95%CI: 0.77–1.74) and type 4 (HR=1.44, 95%CI: 0.84–2.45) trajectories (Table 2). Subgroup analysis showed

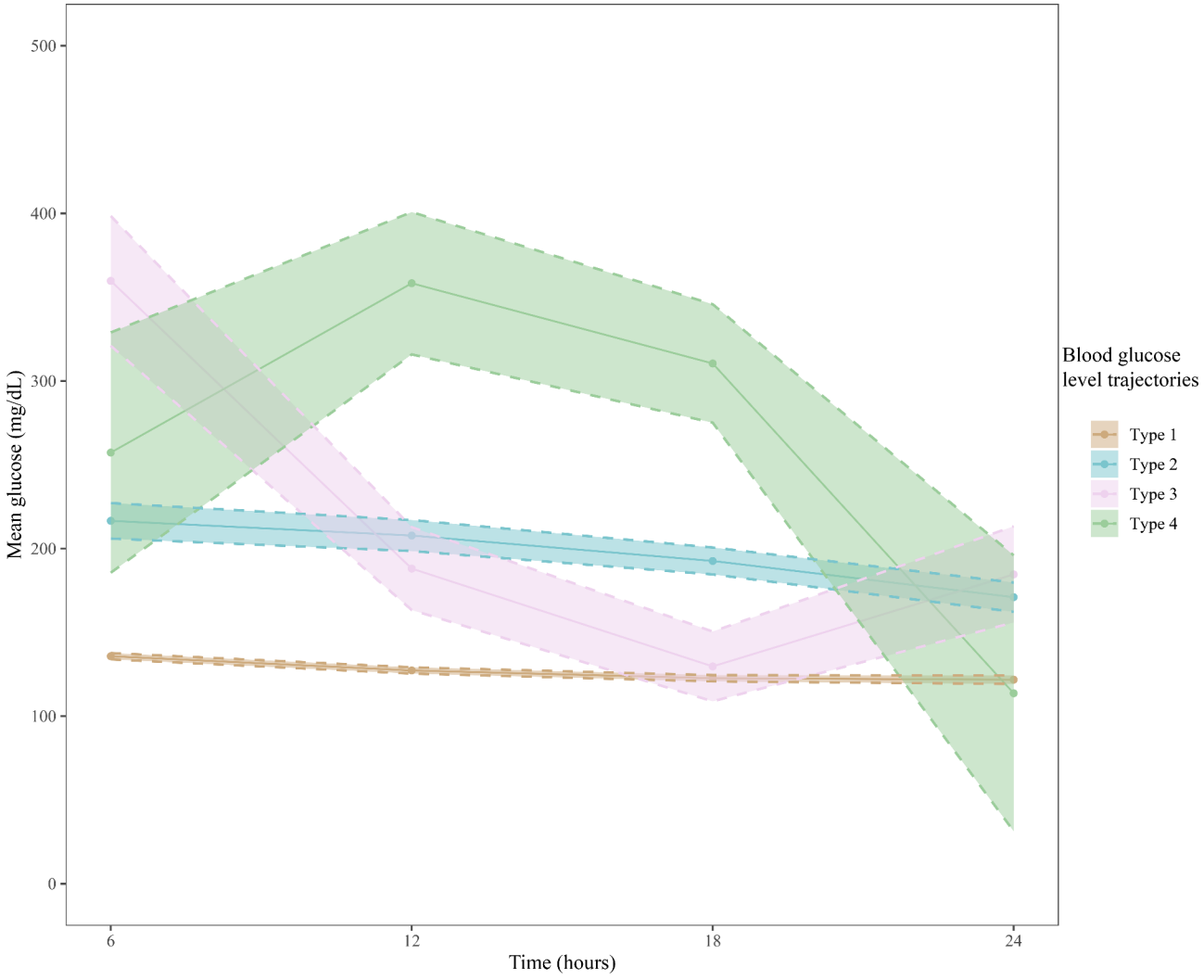

Fig. 2 Trajectory of blood glucose levels within 24 h of admission in patients with acute ischemic stroke (AIS). Type 1, low level-stable trend; Type 2, moderate level-stable trend; Type 3, high level-decreasing-increasing trend; Type 4, moderate level-increasing-decreasing trend

that type 2 blood glucose level trajectory was observed to be associated with a higher risk of 30-day mortality in patients aged ≥ 65 years (HR = 1.37, 95%CI: 1.05–1.79), female (HR = 1.42, 95%CI: 1.05–1.94), with (HR = 1.44, 95%CI: 1.02–2.02) or without (HR = 1.42, 95%CI: 1.01–1.99) diabetes, and not using insulin (HR = 2.80, 95%CI: 1.43–5.49) (Fig. 3). In addition, type 3 (HR = 2.55, 95%CI: 1.48–4.40) and type 4 (HR = 2.67, 95%CI: 1.43–4.99) trajectories were found to be associated with a higher risk of 30-day mortality in male.

Moreover, the interaction tests between blood glucose level trajectories and subgroup variables were also analyzed. The results demonstrated that female gender can antagonize the mortality risk associated with type 3 (HR = 0.24, 95%CI: 0.11–0.55) and type 4 (HR = 0.17, 95%CI: 0.05–0.63) trajectories. Insulin use can antagonize the mortality risk related to type 2 trajectories (HR = 0.47, 95%CI: 0.26–0.85) (Supplement Table 8).

Discussion

High blood glucose levels are considered to be an important factor affecting adverse outcomes in patients with AIS. This study examined the effect of blood glucose levels at ICU admission and blood glucose level trajectories on the risk of 30-day mortality in patients with AIS. The results found that high blood glucose levels at ICU admission were related to a higher risk of 30-day mortality only among patients aged < 65 years or with diabetes. For blood glucose level trajectories, patients with a moderate level-stable trend glucose level trajectory (type 2) had an increased risk of 30-day mortality compared to those with a low level-stable trend glucose level trajectory (type 1), and this relationship was observed in patients aged ≥ 65 years, female, with or without diabetes, and not using insulin.

Stress hyperglycemia is a common complication in patients with AIS [5, 6]. Hyperglycemic environment can

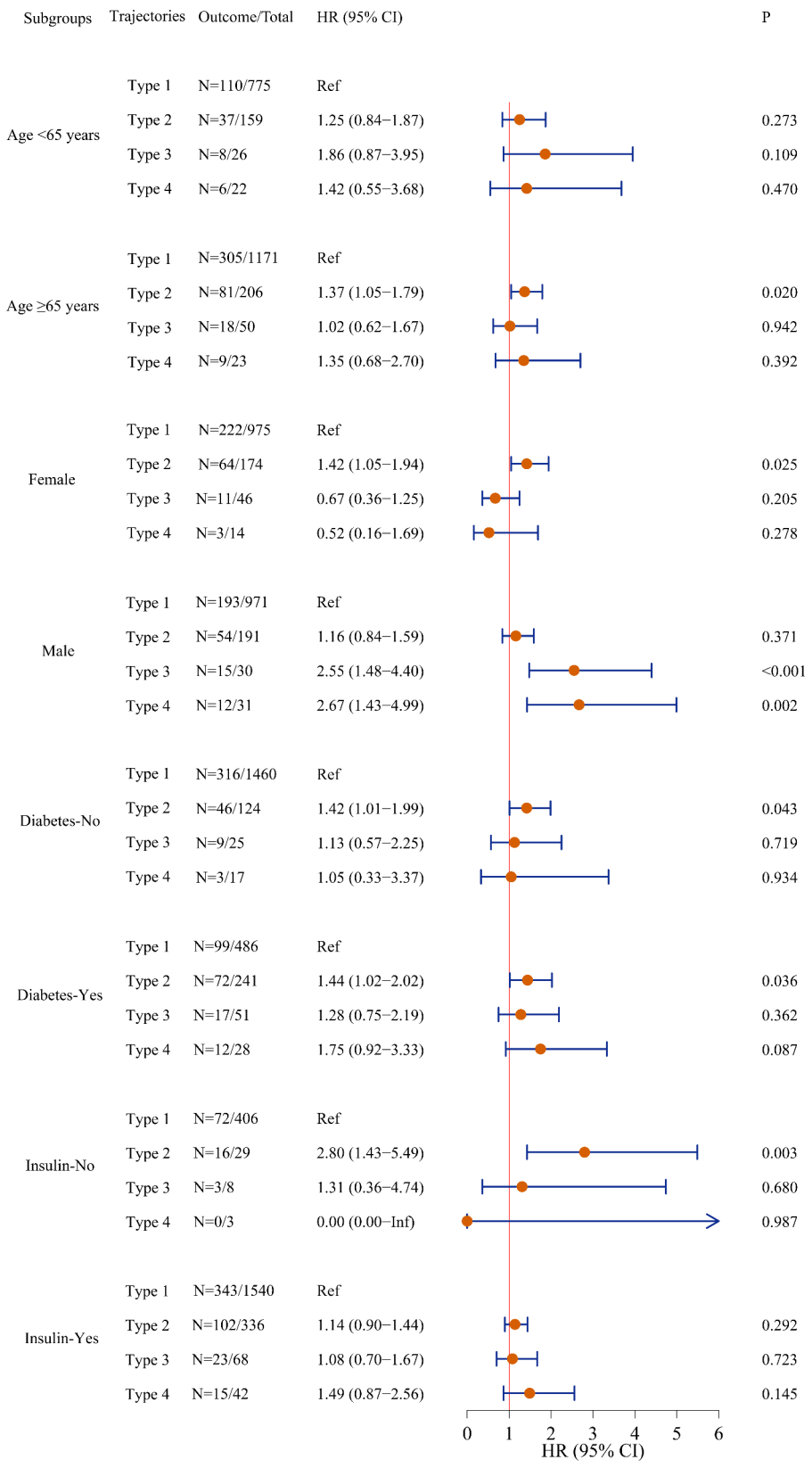

Fig. 3 The association of blood glucose level trajectories with the risk of 30-day mortality in different subgroups of the population. Type 1, low level-stable trend; Type 2, moderate level-stable trend; Type 3, high level-decreasing-increasing trend; Type 4, moderate level-increasing-decreasing trend

exacerbate brain tissue injury and edema in AIS patients, increase infarct size, reduce the effectiveness of thrombolysis and thrombus retrieval, affect the recovery of brain function, and increase mortality [23–25]. Hyperglycemia persisting for 24 h or longer is an independent predictor of adverse clinical outcomes and mortality in patients with AIS [26, 27]. Tziomalos et al. showed that stress hyperglycemia is one of the independent predictors of in-hospital mortality in patients with AIS, but stress hyperglycemia does not seem to be directly related to the prognosis of AIS [28]. The current study examined the impact of blood glucose levels at ICU admission and blood glucose level trajectories on the risk of 30-day mortality in patients with AIS. Our results found that patients with a moderate level-stable trend glucose level trajectory (type 2) had an increased risk of 30-day mortality [vs. low level-stable trend glucose level trajectory (type 1)], but this relationship was not observed in patients with high level-decreasing-increasing trend glucose level trajectory (type 3) and moderate level-increasing-decreasing trend glucose level trajectory (type 4).

Although the type 3 and type 4 trajectories had higher blood glucose levels (>250 mg/dL) on admission, they returned to relatively low levels (<190 mg/dL) over the following 24 h. This may suggest that patients with type 3 and type 4 trajectories are more sensitive to interventions through which blood glucose levels can be lowered as quickly as possible. However, although patients with type 2 trajectories had slightly lower admission glucose levels (>200 mg/dL) than patients with types 3 and 4, the blood glucose level of patients with the type 2 trajectory was always around 200 mg/dL in the following 24 h, and the decrease was not significant. This may indicate that the intervention did not significantly reduce blood glucose levels in patients with type 2 trajectory, which may also explain why patients with type 2 trajectory are associated with a higher 30-day mortality risk. However, no previous studies have reported the effect of blood glucose level trajectories after ICU admission on the risk of 30-day mortality in patients with AIS, and we were unable to compare our blood glucose level trajectory with previous studies. For the effects of long-term hyperglycemia, a 6-year prospective cohort study demonstrated a higher risk of all-cause mortality in the general population in individuals with low-increase and high-increase glycemic trajectories, even if the individuals had normal blood glucose levels at baseline [12]. Several studies have reported the mechanisms of hyperglycemia after ischemic stroke [29]. First, the high incidence of hyperglycemia after ischemic stroke may be related to preexisting abnormalities of glucose metabolism (e.g., insulin resistance). Second, stroke causes a global stress response with activation of the hypothalamic-pituitary-adrenal (HPA) axis [30]. Activation of this complex neural circuitry leads to an increase in serum glucocorticoid (including cortisol) levels and activation of the sympathetic autonomic nervous system, leading to an increase in catecholamine release, and these promote glycogenolysis, gluconeogenesis, proteolysis, and lipolysis, which in turn lead to excess glucose production [29, 31].

Changes in blood glucose levels may induce the adhesion of inflammatory cytokines to vascular endothelial cells, exacerbating the body's inflammatory response, which in turn affects the prognosis of patients with acute cerebral infarction [32]. Hyperglycemia may contribute to the poor prognosis of patients with AIS through several mechanisms. First, hyperglycemia may be directly toxic to ischemic brain tissue (e.g., lactate accumulation and intracellular acidosis) [33], where the development of intracellular acidosis can lead to the expansion of cerebral infarct size. Second, hyperglycemia may affect the prognosis of AIS through endothelial dysfunction. Hyperglycemia attenuates endothelium-dependent vasodilation and insulin secretion, and reduced insulin secretion leads to reduced peripheral glucose uptake and elevated circulating free fatty acids, which may further impair endothelium-dependent vasodilation [34]. Finally, hyperglycemia disrupts the blood-brain barrier after cerebral infarction and promotes hemorrhagic transformation [35, 36]. Under hyperglycemic conditions, increased oxidative and nitrative stress alters tight junction proteins and structures (e.g., decreased levels of occludin), thereby compromising the integrity of the blood-brain barrier [37, 38]. In addition, acute blood glucose levels increase neuronal and vascular damage in ischemic stroke patients, leading to a clinical adverse outcome [39–41].

This study was the first to analyze the impact of short-term longitudinal blood glucose level change trajectories on the 30-day mortality risk in patients with AIS, which fills a gap in the impact of short-term glucose trajectories on short-term mortality in AIS patients admitted to the ICU. Blood glucose level trajectories reflect the dynamic changes in blood glucose levels and are superior to monitoring blood glucose levels at a single time point (e.g., baseline). Nevertheless, the present study also has several limitations. First, this study was based on single-center data and required multiple measurements of blood glucose levels to construct the trajectories, so some selection bias is inevitable. Second, AIS-related features such as infarct site and volume could not be included due to limitations in recording in the MIMIC database. Third, we only analyzed the prognostic impact of blood glucose level trajectories in AIS patients within 24 h of admission, and the prognostic impact of blood glucose level trajectories over a longer period of time on AIS patient needs to be further analyzed.

Conclusions

The current study analyzed the effect of blood glucose level trajectories on the risk of 30-day mortality in patients with AIS. The results showed that patients with consistently high blood glucose levels within 24 h of admission increased the risk of 30-day mortality. However, a rapid downward trend in blood glucose level trajectory within 24 h after admission in patients with high blood glucose levels on admission did not affect the 30-day mortality risk. Subsequent studies may need to investigate the effect of long-term longitudinal blood glucose level trajectories on the risk of mortality in patients with AIS.

Abbreviations

AIS	Acute ischemic stroke
MIMIC	Medical Information Mart for Intensive Care
ICU	Intensive care unit
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
SOFA	Sequential Organ Failure Assessment
GCS	Glasgow Coma Scale
CCI	Charlson comorbidity index
SPO_2	Oxyhemoglobin saturation
WBC	White blood cells
RDW	Red blood cell distribution width
BUN	Blood urea nitrogen
INR	International normalized ration
PT	Prothrombin time
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01482-x.

Supplementary Material 1

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Not applicable.

Author contributions

Li Li and Zhijun Meng designed the study. Li Li wrote the manuscript. Xiaolian Xing, Qian Li, and Qinqin Zhang collected, analyzed, and interpreted the data. Zhijun Meng critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available in the MIMIC-III and MIMIC-IV, https://mimic.physionet.org/iii/, and https://mimic.physionet.org/iv/.

Declarations

Ethics approval and consent to participate

The requirement of ethical approval for this was waived by the Institutional Review Board of Shanxi Provincial People's Hospital, because the data was accessed from MIMIC database (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Shanxi Provincial People's Hospital due to retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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