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Association between lactate dehydrogenase levels and all-cause mortality in ICU patients with heart failure: a retrospective analysis of the MIMIC-IV database

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Abstract

Background Heart failure (HF) patients admitted to the intensive care unit (ICU) often face high short-term mortality rates. This study aims to investigate the relationship between lactate dehydrogenase (LDH) levels and all-cause mortality in critically ill patients with HF.

Methods Data from the MIMIC-IV database were extracted for subjects eligible for HF diagnosis. We utilized the restricted cubic spline (RCS) method, Kaplan-Meier (K-M) survival curves, and Cox regression analysis to assess the association between lactate dehydrogenase (LDH) levels and all-cause mortality in HF patients. Overlap weighting (OW) and subgroup analysis were employed to enhance the robustness and reliability of the study.

Results A total of 3,065 subjects were enrolled in this study. RCS analysis revealed a nonlinear relationship between LDH levels and the risk of all-cause mortality in critically ill patients with HF, with a hazard ratio (HR) > 1 when LDH exceeded 315 U/L. The K-M survival curve indicated lower survival rates and shorter survival times in subjects with LDH ≥ 315 U/L. Elevated LDH levels were independently associated with increased in-hospital and 1-year mortality rates, with adjusted HR of 1.39 (95% CI: 1.16, 1.67) and 1.29 (95% CI: 1.14, 1.45), respectively. The results remained consistently robust in the OW analyses.

Conclusions Elevated LDH levels were significantly associated with an increased risk of all-cause mortality in ICU-admitted HF patients. Further randomized trials are needed to confirm this association.

Keywords Lactate dehydrogenase, Heart failure, Intensive care units, Mortality, MIMIC-IV

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Introduction

Heart failure (HF) is a global public health issue affecting the health and quality of life of more than 64 million individuals [1]. It arises from various causes and manifests as a progressive clinical syndrome characterized by inadequate cardiac pumping and altered hemodynamics. HF involves pathological changes such as decreased oxidative phosphorylation and increased glycolytic pathways [2, 3]. Despite significant advances in recognizing and treating HF in modern medicine, its prevalence and rates of rehospitalization remain elevated and are strongly linked to high mortality rates [4]. In recent decades, advances in evidence-based pharmacological treatments, implanted devices, and innovative care models have substantially improved outcomes for HF with reduced ejection fraction, leading to decreased mortality rates across all age groups [5, 6]. Nonetheless, the prognosis of critically ill patients with HF remains uncertain. This underscores the critical importance of providing reliable prognostic markers to guide clinical decisions and improve patient care.

Currently, natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are globally recognized markers widely used in diagnosing HF [7]. However, plasma BNP levels are less sensitive for the diagnosis of HF when patients present with renal insufficiency, atrial fibrillation, and inflammation [8–10]. This underscores the pressing need to explore additional reliable predictors of HF. In recent years, dysregulation of glycolytic pathways in cardiovascular disease research has emerged as a significant study area, offering valuable insights into various cardiovascular pathologies [11]. Lactate dehydrogenase (LDH), an enzyme found extensively in different tissues of the body, notably in high concentrations in the heart, kidneys, skeletal muscle, and liver, has shown the potential to improve patient care in HF significantly [12]. Its role in anaerobic glucose metabolism and gluconeogenesis makes it a promising tool for the early identification of high-risk individuals and the optimization of therapeutic strategies [13]. Currently, the measurement of LDH levels is valuable in assessing the prognosis of patients with tumors, cerebral hemorrhage, and liver disease [14, 15]. However, studies investigating its specific role in predicting prognosis in critically ill HF patients are limited and lack confirmation from large-scale studies.

This study aims to explore the relationship between LDH levels and all-cause mortality among ICU-admitted critically ill patients with HF, as well as to evaluate the prognostic significance of LDH.

Methods

Data sources and ethics statement

The study utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV), a comprehensive publicly accessible database. This database includes information on patients treated at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. Access to the database was granted after researcher Panxu Guo (record ID: 58462281) completed the National Institutes of Health's online training courses. All data used in this study were anonymized; therefore, informed consent was not necessary. The research protocol was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [16].

Inclusion and exclusion criteria

The MIMIC-IV database (version 2.2) comprises records of 73,181 ICU admissions at BIDMC from 2008 to 2019. Patients diagnosed with heart failure based on the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10) diagnosis codes (see Supplementary Table 1) were included in this study. Inclusion criteria: (1) First ICU admission; (2) Age > 18. Exclusion criteria: (1) Length of ICU stay < 24 h; (2) Participants with missing data for lactate dehydrogenase; (3) LDH levels below the 0.5th percentile or above the 99.5th percentile. Finally, this study included 3,065 patients.

Data extraction

Variables were extracted from the MIMIC-IV database using Structured Query Language (SQL) and PostgreSQL. Six types of variables were included: (1) demographics, (2) comorbidities identified by the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10), (3) vital signs, (4) laboratory values, (5) medications, and (6) scoring systems. To minimize bias, variables with more than 10% missing values were excluded. Variables with less than 10% missing data were imputed using the 'missForest' package in R, employing the random forest algorithm for multiple imputations [17]. Missing data are detailed in Supplementary Fig. 1 demonstrates. The primary outcome assessed in this study was in-hospital mortality, with one-year mortality as a secondary outcome.

Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD), while skewed continuous variables were reported as median with interquartile range (IQR). The normality of distributions was assessed using the Shapiro-Wilk test. Depending on the

distribution type of continuous variables, statistical comparisons were performed using either the Student's t-test or the Mann-Whitney U-test. Categorical variables were expressed as percentages and analyzed using either the chi-square test (χ^2) or Fisher's exact test.

Restricted cubic spline (RCS) analysis using the Cox proportional hazards model was employed to explore the linear or nonlinear relationship between LDH levels. An inflection point of LDH was determined as the threshold to classify the cohort into low and high LDH groups. Kaplan-Meier (K-M) survival curves were used to visually depict the cumulative probability of all-cause mortality across different LDH level groups, with Log-rank tests utilized to compare risk differences between these groups.

We employed multivariate Cox regression modeling to investigate the association between LDH levels and all-cause mortality in ICU patients with heart failure. The selection criteria for confounders included the following: (1) variables with a p-value < 0.05 in univariate analyses; (2) factors identified as significant in previous literature or clinical practice; and (3) variables with variance inflation factors (VIF) < 5, as detailed in Supplementary Table S3. No covariates were adjusted in the initial model. Model 1 accounted for confounders including age, sex, weight, race, cerebrovascular disease, and liver disease. Model 2 further adjusted for heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, oxygen saturation (SpO2), blood urea nitrogen (BUN), potassium, white blood cell count (WBC), partial thromboplastin time (PTT), glucose, use of warfarin, aspirin, vasopressin, norepinephrine, dobutamine, mechanical circulatory support (MCS), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), Charlson Comorbidity Index (CCI), length of hospitalization, length of ICU stay, and cardiogenic shock.

To enhance the reliability of our study results, we utilized the propensity score overlap weighting (OW) method to harmonize the baseline characteristics between the two groups of subjects [18]. OW aims to mitigate baseline characteristic disparities among patients in the high and low LDH groups. The balance of weighted covariates was evaluated using standardized mean difference (SMD), with SMD < 0.2 indicating an appropriate balance between groups. Subsequently, Kaplan-Meier curves and Cox regression analyses were conducted on the weighted cohorts to evaluate LDH's impact on all-cause mortality in HF patients.

To enhance the robustness of our findings, subgroup analyses were conducted to investigate the association between LDH levels and mortality across various subgroups defined by age, gender, race, and comorbidities. Additionally, receiver operating characteristic (ROC) curve analyses were performed to compare the predictive performance of LDH, OASIS, and SAPS II scores for predicting in-hospital mortality in heart failure patients.

Statistical analyses were carried out using R software (version 4.4.1). A significance level of $p < 0.05$ (two-sided) was considered statistically significant.

Results

Baseline characteristics

A total of 3065 HF patients met the screening criteria (see Fig. 1). Detailed baseline patient demographics, including pre- and post-OW of propensity scores, are summarized in Table 1. Table 1 indicates that, compared to the low LDH group, the high LDH group exhibited higher in-hospital and 1-year mortality rates as well as longer hospital stays. Before propensity score weighting, significant differences were observed between the groups in age, race, blood pressure, HR, SAPS II, OASIS, vasopressin, norepinephrine, dobutamine, MCS, cardiogenic shock, specific comorbidities, and laboratory parameters. However, after weighting, these differences were minimized, with SMD between the groups reduced to less than 0.2. Supplementary Fig. 2 illustrates the balanced distribution of most covariates between the high and low LDH groups in the weighted cohort. During the weighting process, a propensity score model was constructed using 26 covariates. OW were then applied based on the estimated propensity scores to reduce disparities between the cohorts.

The association between LDH levels and mortality

The association between LDH levels and mortality was examined using an RCS model, depicted in Fig. 2. A significant nonlinear relationship between LDH levels and all-cause mortality in ICU patients with heart failure was observed in the unadjusted model (P for nonlinearity < 0.001). In the fully adjusted model (Fig. 2C and D), There was also a significant nonlinear relationship between LDH levels and in-hospital mortality (Fig. 2C, P for nonlinearity = 0.001) and 1-year mortality (Fig. 2C, P for nonlinearity < 0.001) in patients with HF. Based on RCS analysis, subjects were stratified into two groups based on LDH values (LDH < 315 U/L vs. LDH ≥ 315 U/L). K-M survival curves also demonstrated a significantly higher all-cause mortality risk in the high LDH group (Log-rank $p < 0.0001$, Fig. 3). To determine if elevated LDH independently predicts all-cause mortality risk in HF patients, univariate and multivariate Cox regression analyses were performed. In univariate models, LDH showed a strong association with increased in-hospital (HR = 1.95, 95% CI: 1.65, 2.31) and 1-year (HR = 1.44, 95% CI: 1.29, 1.60) all-cause mortality. After adjusting for various confounders in multivariate analysis, LDH remained significantly associated with increased in-hospital (HR = 1.39, 95% CI: 1.16, 1.67) and 1-year

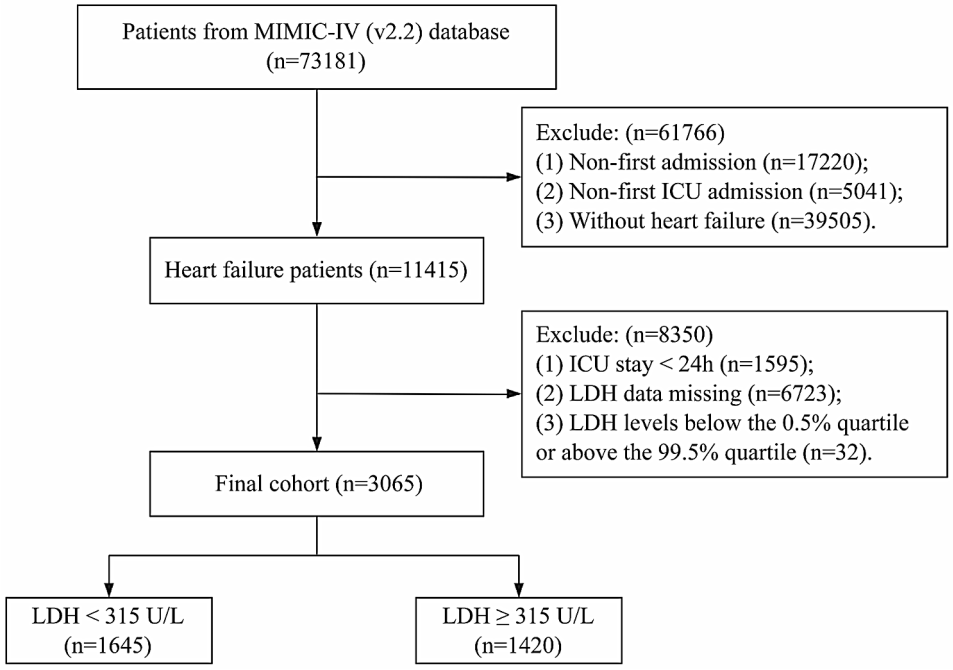

Fig. 1 Flow diagram for patient selection

(HR = 1.29, 95% CI: 1.14, 1.45) all-cause mortality, as presented in Table 2. Supplementary Table 2 displays the associations of various covariates with in-hospital mortality.

Outcomes after OW

To minimize confounding bias, we performed an OW analysis in our study. After overlap weighting, the final analysis included 1532 patients with high LDH and 1532 patients with low LDH. Nearly all covariates were evenly distributed in both groups (Table 1). Weighted Cox regression in fully adjusted models indicated a significantly higher risk of in-hospital mortality (HR = 1.37; 95% CI: 1.13, 1.66) and 1-year mortality (HR = 1.30; 95% CI: 1.14, 1.49) in the high LDH group compared to the low LDH group. The association between high LDH levels and increased all-cause mortality remained statistically significant (Table 2).

Predictive values of LDH and some severity scores for in-hospital mortality

Figure 4 illustrates the predictive values of LDH and several severity scoring systems (OASIS and SAPSII) for in-hospital all-cause mortality, evaluated through ROC curve analysis. LDH (AUC = 0.632, 95% CI: 0.607, 0.657) showed relatively poorer predictive ability compared to SAPSII (AUC = 0.746, 95% CI: 0.724, 0.768) and OASIS (AUC = 0.707, 95% CI: 0.683, 0.731) scores for in-hospital mortality in HF patients, performing at a moderate level overall.

Subgroup analysis

The prognostic utility of LDH in predicting outcomes in critically ill patients with HF was further assessed across various patient subgroups, including age, gender, ethnicity, MCS, comorbidities (hypertension, myocardial infarction, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, diabetes, renal disease, and liver disease) and Cardiogenic shock (Fig. 5). Overall, a positive correlation between LDH levels and all-cause mortality was consistently observed across most subgroups, indicating that higher LDH levels were associated with increased mortality. Significant interactions were noted in the cerebrovascular disease (P for interaction = 0.001) and Cardiogenic shock (P for interaction = 0.008) subgroups. Specifically, LDH levels were more strongly associated with in-hospital mortality in patients without cerebrovascular disease (HR = 1.58, 95% CI: 1.29, 1.94) and patients with combined cardiogenic shock (HR = 1.54, 95% CI: 1.25, 1.91).

Discussion

This study identified a nonlinear relationship between baseline LDH levels and short- and long-term all-cause mortality among ICU patients with heart failure. Elevated LDH levels were significantly associated with a higher risk of death. Even after adjusting for confounding factors, in-hospital and one-year mortality rates remained consistently higher in the high-LDH group than in the low-LDH group. To minimize confounding bias, we employed OW analysis for a more accurate assessment

Table 1 Demographic characteristics of heart failure patients before and after overlapping weighting of propensity scores

Characteristics	Overall	Original cohort			Weight cohort		
		LDH < 315 U/L	LDH ≥ 315 U/L	SMD	LDH < 315 U/L	LDH ≥ 315 U/L	SMD
N	3065	1645	1420	-	1532	1532	-
Age, years	72.0 (61.0, 81.0)	73.0 (62.0, 82.0)	70.5 (60.0, 79.0)	0.183	71.0 (60.0, 81.0)	72.0 (61.0, 81.0)	< 0.001
Gender, n (%)							
Female	1317 (43.0%)	704 (42.8%)	613 (43.2%)	0.008	622 (40.6%)	726 (47.4%)	0.137
Male	1748 (57.0%)	941 (57.2%)	807 (56.8%)		911 (59.4%)	807 (52.6%)	
Weight, kg	80.0 (67.0, 96.7)	80.5 (67.0, 98.3)	80.0 (66.6, 95.4)	0.076	80.5 (67.4, 99.0)	78.1 (65.0, 94.0)	0.156
Ethnicity, n (%)							
White	1995 (65.1%)	1107 (67.3%)	888 (62.5%)	0.100	993 (64.8%)	993 (64.8%)	< 0.001
Other	1070 (34.9%)	538 (32.7%)	532 (37.5%)		539 (35.2%)	539 (35.2%)	
Hypertension, n (%)	778 (25.4%)	419 (25.5%)	359 (25.3%)	0.004	395 (25.7%)	392 (25.6%)	0.004
Myocardial infarct, n (%)	1120 (36.5%)	476 (28.9%)	644 (45.4%)	0.345	562 (36.7%)	562 (36.7%)	< 0.001
Peripheral vascular disease, n (%)	465 (15.2%)	252 (15.3%)	213 (15.0)	0.009	235 (15.3%)	226 (14.8%)	0.016
Cerebrovascular disease, n (%)	426 (13.9%)	235 (14.3%)	191 (13.5%)	0.024	211 (13.8%)	205 (13.4%)	0.011
Chronic pulmonary disease, n (%)	1065 (34.7%)	610 (37.1%)	455 (32.0%)	0.106	527 (34.4%)	527 (34.4%)	< 0.001
Diabetes, n (%)	1234 (40.3%)	696 (42.3%)	538 (37.9%)	0.09	658 (42.9%)	579 (37.8%)	0.105
Renal disease, n (%)	1224 (39.9%)	701 (42.6%)	523 (36.8%)	0.118	603 (39.4%)	603 (39.4%)	< 0.001
Liver disease, n (%)	448 (14.6%)	214 (13.0%)	234 (16.5%)	0.098	217 (14.1%)	229 (15.0%)	0.023
SBP, mmHg	112.0 (103.0, 124.0)	114.0 (104.0, 127.0)	110.0 (101.0, 121.0)	0.238	112.0 (103.0, 124.0)	112.0 (102.0, 123.0)	< 0.001
DBP, mmHg	61.0 (54.0, 68.0)	60.0 (54.0, 68.0)	61.0 (55.0, 69.0)	0.104	61.0 (54.0, 69.0)	61.0 (54.0, 68.0)	< 0.001
HR, beats/min	85.0 (74.0, 98.0)	83.0 (72.0, 96.0)	87.0 (76.0, 99.0)	0.228	85.0 (73.0, 98.0)	85.3 (75.0, 97.0)	< 0.001
RR, times/min	20.0 (18.0, 23.0)	20.0 (17.0, 22.0)	20.0 (18.0, 23.0)	0.203	20.0 (18.0, 23.0)	20.0 (18.0, 23.0)	< 0.001
Temperature, ℃	36.8 (36.5, 37.0)	36.7 (36.5, 37.0)	36.8 (36.6, 37.1)	0.064	36.7 (36.5, 37.0)	36.8 (36.6, 37.1)	0.030
SPO_2, %	97.0 (95.0, 98.0)	97.0 (95.0, 98.0)	97.0 (95.0, 98.0)	0.084	97.0 (95.0, 98.0)	97.0 (95.0, 98.0)	0.021
BUN, mg/dL	30.0 (19.0, 49.0)	29.0 (19.0, 47.0)	31.0 (20.0, 51.0)	0.088	30.0 (19.0, 47.0)	30.0 (20.0, 50.0)	0.055
Serum creatinine, mg/dl	1.4 (0.9, 2.2)	1.3 (0.9, 2.1)	1.4 (1.0, 2.2)	0.081	1.3 (0.9, 2.1)	1.4 (1.0, 2.2)	0.046
Sodium, mmol/L	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	0.002	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	0.089
Potassium, mmol/L	4.2 (3.8, 4.7)	4.2 (3.8, 4.7)	4.3 (3.9, 4.9)	0.191	4.2 (3.8, 4.7)	4.2 (3.8, 4.8)	< 0.001
WBC, K/uL	11.2 (7.9, 15.8)	10.0 (7.2, 13.7)	12.7 (9.1, 17.7)	0.316	10.7 (7.6, 15.4)	11.7 (8.3, 16.0)	< 0.001
RBC, m/uL	3.5 (3.0, 4.1)	3.5 (2.9, 4.0)	3.6 (3.0, 4.2)	0.144	3.5 (3.0, 4.1)	3.5 (3.0, 4.1)	< 0.001
Hemoglobin, g/dL	10.4 (8.8, 12.0)	10.2 (8.7, 11.7)	10.6 (8.9, 12.4)	0.194	10.4 (8.8, 12.0)	10.4 (8.7, 12.0)	< 0.001
Platelet, K/uL	192.0 (137.0, 261.0)	192.0 (143.0, 260.0)	191.0 (131.0, 262.0)	0.064	192.4 (142.0, 264.0)	186.0 (127.0, 258.0)	0.130
INR	1.4 (1.2, 1.8)	1.4 (1.2, 1.8)	1.4 (1.2, 1.9)	0.158	1.4 (1.2, 1.8)	1.4 (1.2, 1.8)	< 0.001
PT, seconds	15.2 (13.1, 19.7)	14.9 (12.9, 18.9)	15.5 (13.3, 20.7)	0.161	15.1 (13.0, 19.5)	15.3 (13.1, 19.7)	< 0.001
PTT, seconds	34.0 (28.6, 45.7)	33.0 (28.4, 42.0)	35.9 (28.7, 51.8)	0.296	33.9 (28.8, 44.7)	34.0 (28.2, 45.8)	< 0.001
Glucose, mmol/L	7.6 (6.3, 9.8)	7.3 (6.1, 9.3)	8.0 (6.6, 10.3)	0.242	7.4 (6.2, 9.7)	7.6 (6.3, 9.8)	< 0.001
Warfarin, n (%)	918 (30.0%)	491 (29.8%)	427 (30.1%)	0.005	473 (30.9%)	449 (29.3%)	0.035
Aspirin, n (%)	2035 (66.4%)	1065 (64.7%)	970 (68.3%)	0.076	1012 (66.0%)	1012 (66.0%)	< 0.001
Vasopressin, n (%)	508 (16.6%)	181 (11.0%)	327 (23.0%)	0.324	238 (15.5%)	238 (15.5%)	< 0.001
Norepinephrine, n (%)	1225 (40.0%)	542 (32.9%)	683 (48.1%)	0.312	604 (39.4%)	604 (39.4%)	< 0.001
Dobutamine, n (%)	261 (8.5%)	69 (4.2%)	192 (13.5%)	0.333	104 (6.8%)	104 (6.8%)	< 0.001
RRT, n (%)	1806 (58.9%)	949 (57.7%)	857 (60.4%)	0.054	874 (57.1%)	918 (59.9%)	0.057
Invasive ventilation, n (%)	1118 (36.5%)	502 (30.5%)	616 (43.4%)	0.269	525 (34.2%)	564 (36.8%)	0.053
Non invasive ventilation, n (%)	332 (10.8%)	204 (12.4%)	128 (9.0%)	0.110	197 (12.9%)	141 (9.2%)	0.117
MCS, n (%)	262 (8.5%)	72 (4.4%)	190 (13.4%)	0.321	107 (7.0%)	107 (7.0%)	< 0.001
SAPSII	40.0 (32.0, 50.0)	39.0 (32.0, 47.0)	42.0 (34.0, 53.0)	0.304	40.0 (33.0, 50.0)	40.0 (32.0, 50.0)	< 0.001
OASIS	33.0 (27.0, 39.0)	32.0 (27.0, 38.0)	34.0 (28.0, 41.0)	0.243	33.0 (27.0, 39.0)	33.0 (27.0, 39.0)	< 0.001
CCI	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	0.088	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	0.013
Hospital length of stay, days	9.7 (5.9, 15.8)	9.0 (5.9, 14.6)	10.3 (6.0, 17.5)	0.145	9.8 (6.1, 15.8)	9.8 (5.9, 16.2)	< 0.001
Cardiogenic shock, n (%)	531 (17.3%)	151 (9.2%)	380 (26.8%)	0.470	223 (14.6%)	223 (14.6%)	< 0.001
ICU length of stay, days	3.3 (2.0, 6.1)	2.9 (1.8, 5.2)	4.0 (2.2, 7.2)	0.264	3.2 (1.9, 6.0)	3.5 (2.0, 6.1)	< 0.001

Table 1 (continued)

Characteristics	Overall	Original cohort			Weight cohort		
		LDH < 315 U/L	LDH ≥ 315 U/L	SMD	LDH < 315 U/L	LDH ≥ 315 U/L	SMD
In-hospital mortality, n (%)	580 (18.9%)	219 (13.3%)	361 (25.4%)	0.310	234.1 (15.3%)	334.0 (21.8%)	0.168
1-year mortality, n (%)	1309 (42.7%)	634 (38.5%)	675 (47.5%)	0.182	611.2 (39.9%)	705.7 (46.0%)	0.125

Data: N (%) or median (IQR); SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SPO_2: saturation of peripheral oxygen; BUN: blood urea nitrogen; WBC: white blood cell count; RBC: red blood cell count; INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time; RRT: renal replacement therapy; MCS: mechanical circulatory support; SAPSII: simplified acute physiology score II; OASIS: oxford acute severity of illness score; CCI: Charlson comorbidity index

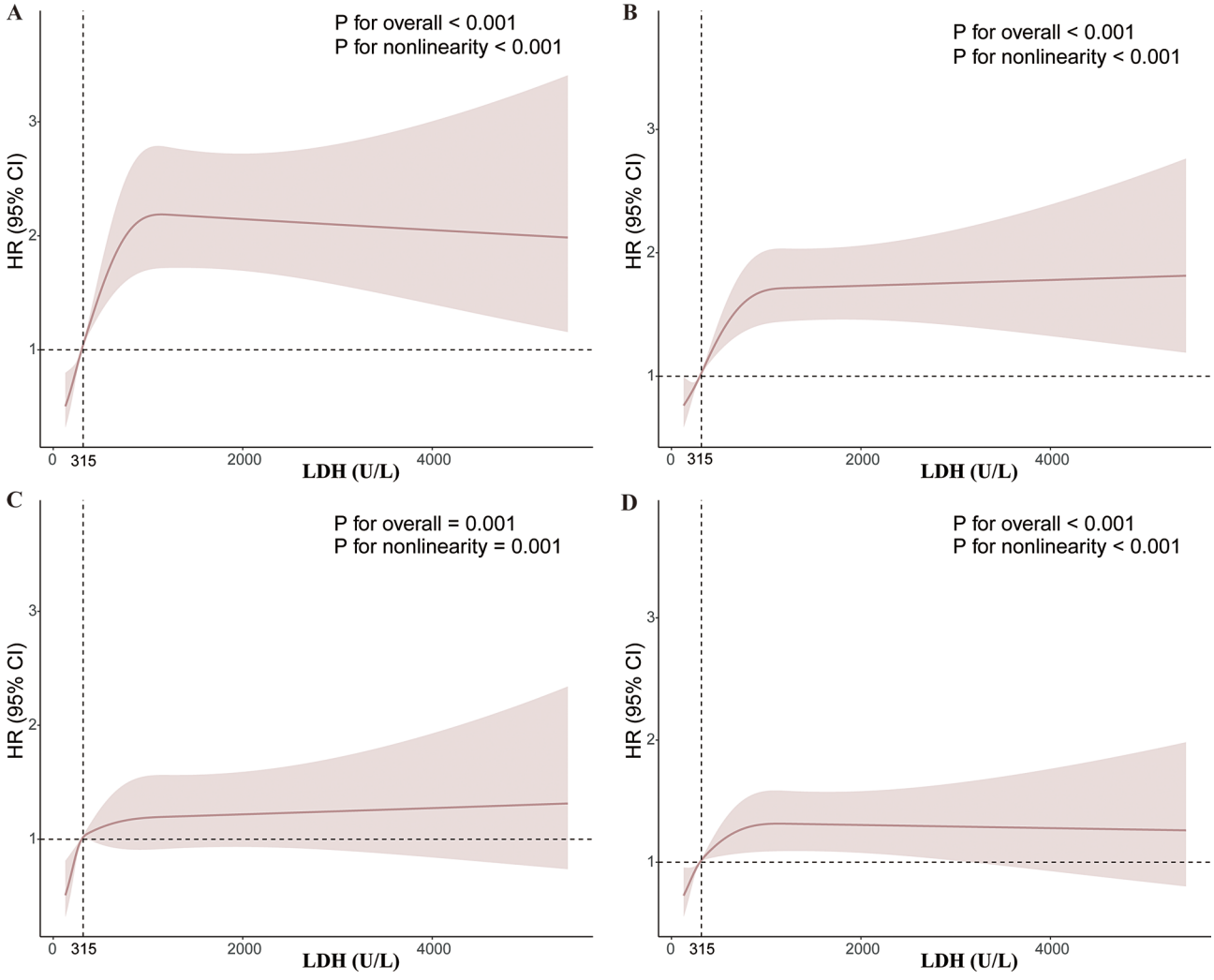

Fig. 2 Relationship between lactate dehydrogenase (LDH) levels and mortality in heart failure patients. Unadjusted in-hospital mortality (**A**), 1-year mortality (**B**), and fully adjusted in-hospital mortality (**C**), 1-year mortality (**D**). HR: hazard ratio; CI: confidence interval

of survival differences based on LDH levels. The results support the significant association between LDH levels and all-cause mortality.

LDH is a widely distributed cellular enzyme that plays a crucial role in glycolysis and anaerobic metabolism [19]. Its stable structure and minimal amino acid sequence variations make it an ideal target for designing and regulating catalytic activity and expression. LDH catalyzes the conversion of lactate to pyruvate and facilitates the NADH/NAD + redox reaction during glycolysis. LDH exists as a tetramer composed of muscle (M) and heart (H) subunits, and it is categorized into five isozymes (LDH-1 to LDH-5), each exhibiting distinct enzymatic activities in vitro [20]. Animal studies indicate that mammary muscle exhibits the highest LDH activity, followed by the myocardium, liver, and serum, while lower activity is observed in the lung and pancreas [21].

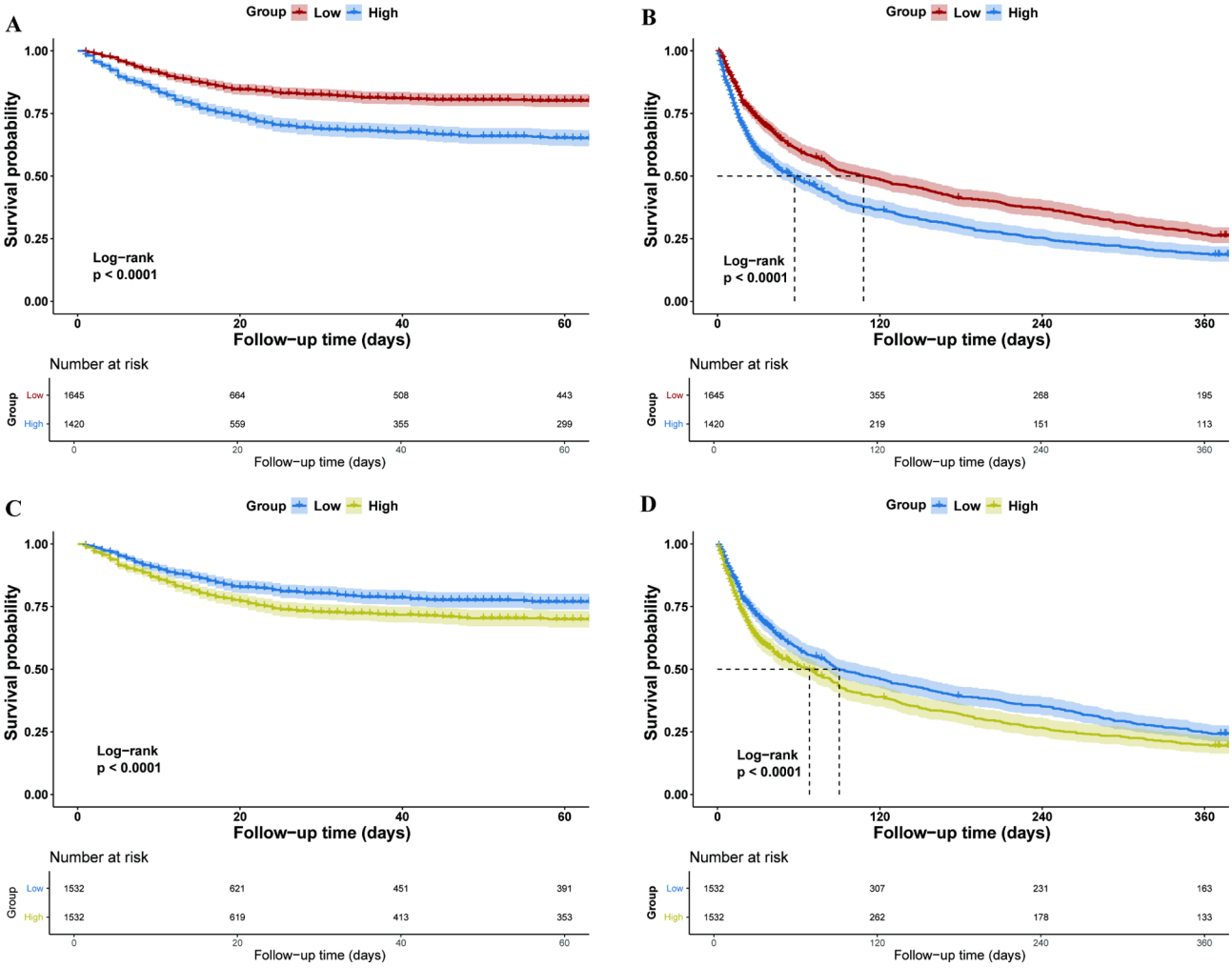

Fig. 3 Kaplan-Meier survival curves for patients with low (LDH < 315 U/L) and high (LDH ≥ 315 U/L) lactate dehydrogenase (LDH) during hospitalization (**A**, **C**) and at 1-year follow-up (**B**, **D**). Panels (**A**-**B**) show raw cohort results, while panels (**C**-**D**) display overlap-weighted adjusted results

Variations in LDH isoenzymes have been correlated with the severity of heart failure [22]. Elevated serum LDH levels reflect tissue catabolism and are associated with various pathological conditions, including blood disorders, cancer, tissue infarction, liver disease, and respiratory conditions [15, 23–25]. Clinical studies have identified LDH as a potential prognostic marker of both short- and long-term all-cause mortality in patients with acute decompensated heart failure [26]. Studies have also demonstrated that elevated LDH levels are correlated with the severity of idiopathic pulmonary hypertension, progression to right heart failure, and higher mortality rates [27]. Furthermore, prior studies indicate that LDH levels reflect the extent of myocardial injury and cardiac functional status, providing prognostic value that may be superior to other markers of myocardial injury [28, 29].

Our study demonstrated that elevated LDH levels serve as an independent risk factor for in-hospital mortality among ICU patients with heart failure, consistent with prior findings [26]. Elevated LDH levels reflect severe cellular damage and metabolic disturbances, heightening the risk of complications and contributing to higher in-hospital mortality [30]. The LDH risk threshold identified in this study was 315 U/L, aligning with previous studies, although variations in specific values were observed due to differences in patient cohorts. For instance, Zeng et al. [31] reported an LDH threshold of 328 U/L in patients undergoing cardiac surgery, achieving an AUC of 0.795 for predicting in-hospital mortality. Lin et al. [32] observed that LDH ≥ 335 U/L was significantly associated with higher ICU mortality in patients with cardiac arrest (59.6% vs. 44.1%), highlighting its prognostic value in critically ill populations. Notably, Zhou et al. [33] reported that LDH levels typically remain below 200 U/L in healthy populations. Higher thresholds (315–335 U/L) in this and similar studies of critically ill patients likely reflect the substantial metabolic burden and tissue damage typical of ICU populations [34]. Overall,

Table 2 Multifactorial COX regression modeling of the relationship between LDH groups and mortality in patients with heart failure

	Variable	Crude model		Model 1		Model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Original cohort	**In-hospital mortality**						
	LDH group						
	< 315 U/L	1 (ref)		1 (ref)		1 (ref)	
	≥ 315 U/L	1.95 (1.65, 2.31)	< 0.001	2.01 (1.70, 2.38)	< 0.001	1.39 (1.16, 1.67)	< 0.001
	1-year mortality						
	LDH group						
	< 315 U/L	1 (ref)		1 (ref)		1 (ref)	
	≥ 315 U/L	1.44 (1.29, 1.60)	< 0.001	1.49 (1.33, 1.66)	< 0.001	1.29 (1.14, 1.45)	< 0.001
Weighted cohort	**In-hospital mortality**						
	LDH group						
	< 315 U/L	1 (ref)		1 (ref)		1 (ref)	
	≥ 315 U/L	1.41 (1.17, 1.70)	< 0.001	1.40 (1.16, 1.69)	< 0.001	1.37 (1.13, 1.66)	0.001
	1-year mortality						
	LDH group						
	< 315 U/L	1 (ref)		1 (ref)		1 (ref)	
	≥ 315 U/L	1.25 (1.11, 1.41)	< 0.001	1.25 (1.11, 1.41)	< 0.001	1.30 (1.14, 1.49)	< 0.001

Crude model: Not adjusted for any variables

Model 1: Adjusted for Age, Gender, Weight, Ethnicity, Cerebrovascular Disease, and Liver Disease

Model 2: Adjusted for all variables in Model 1, plus HR, RR, SBP, DBP, Temperature, SpO_2, BUN, Potassium, WBC, PTT, Glucose, Warfarin, Aspirin, Vasopressin, Norepinephrine, Dobutamine, MCS, SAPSII, OASIS, CCI, Hospital Length of Stay, ICU Length of Stay, and Cardiogenic Shock

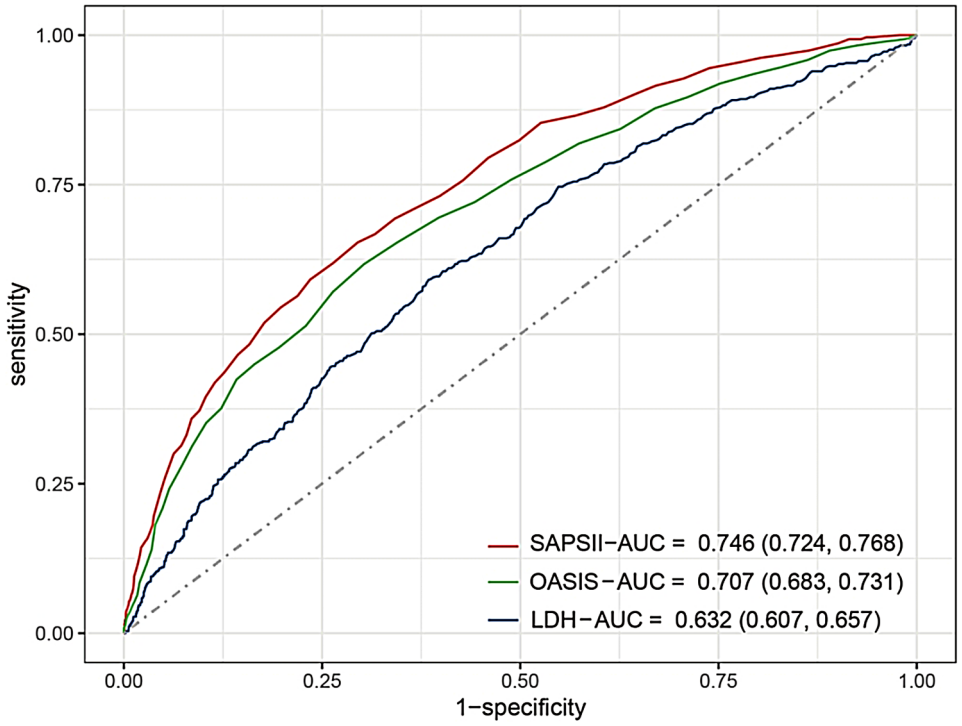

Fig. 4 ROC curve of LDH, OASIS score, and SAPS II score in predicting in-hospital mortality in patients with heart failure. LDH: lactate dehydrogenase; OASIS: Oxford Acute Severity of Illness Score; SAPS II: Simplified Acute Physiology Score II

the prognostic value of LDH as a broadly applicable biomarker has been validated across various pathological contexts.

Subgroup analyses further revealed that LDH levels were more predictive in patients without cerebrovascular disease and in those with cardiogenic shock (P for interaction < 0.05). Elevated LDH levels were significantly associated with in-hospital mortality in patients without cerebrovascular disease. In contrast, no such association was observed in patients with cerebrovascular

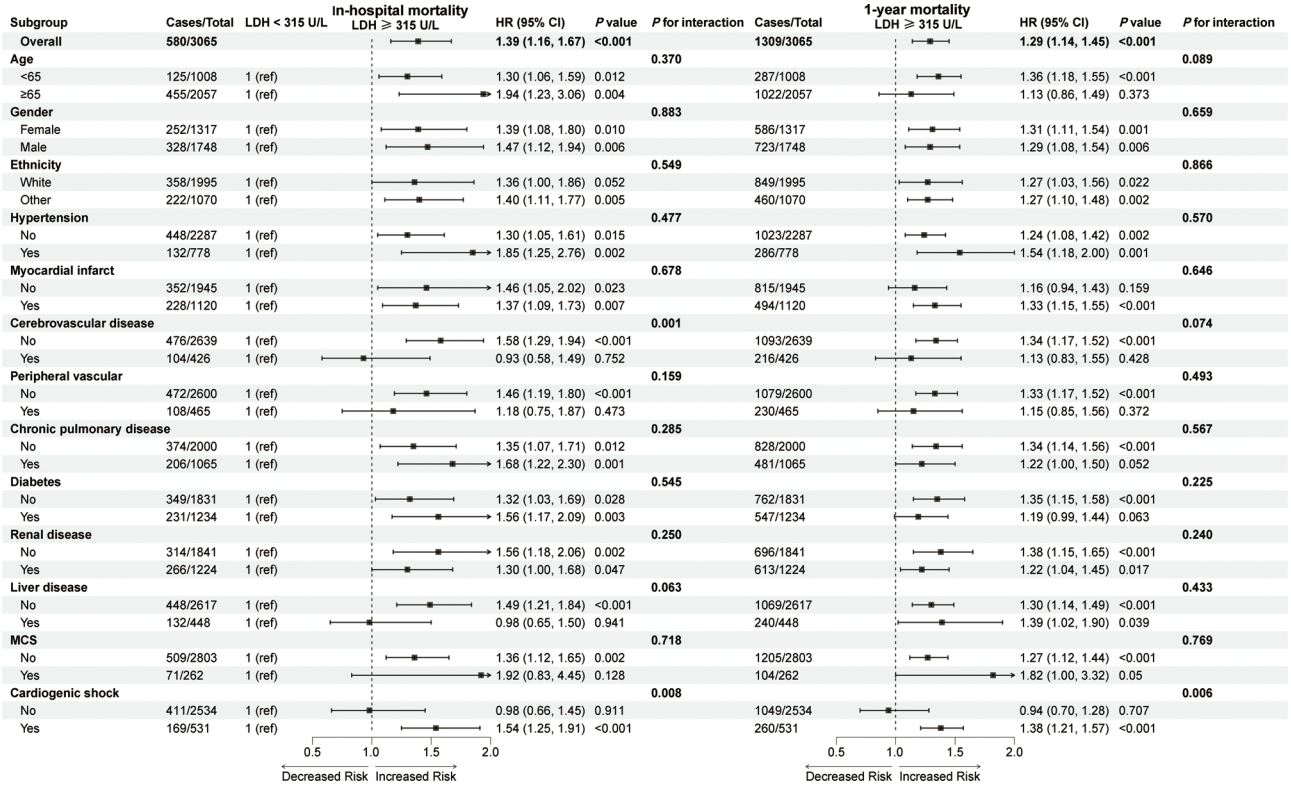

Fig. 5 Subgroup analysis of the association between lactate dehydrogenase (LDH) levels and in-hospital and 1-year mortality in the original cohort. All subgroups were adjusted using the variables in Model 2

comorbidities, possibly due to complex pathological processes that attenuate the predictive role of LDH [35]. Similarly, in patients with cardiogenic shock, elevated LDH levels were strongly associated with both in-hospital and one-year mortality, highlighting their clinical relevance in high-risk subgroups. Moreover, LDH demonstrated moderate predictive value for assessing in-hospital mortality risk in ICU heart failure patients, with an AUC of 0.632. As a simple and readily accessible biomarker, LDH holds promise for the early identification of high-risk patients and the optimization of therapeutic strategies.

This study has several notable strengths. First, it utilized data from the large and high-quality MIMIC-IV ICU database, which provides a comprehensive and diverse sample of critically ill patients, thereby enhancing the generalizability of the findings. Second, the study focused on exploring the association between baseline LDH levels and mortality risk in patients with heart failure, offering a deeper understanding of the relationship between these variables. Additionally, the use of OW analysis allowed for a more robust control of confounding factors, improving the reliability of our results. Furthermore, the identification of an LDH threshold of 315 U/L for predicting in-hospital mortality adds valuable clinical insight and contributes to the growing body of evidence supporting LDH as a relevant biomarker for critically ill patients.

Despite the strengths of our study, several limitations warrant cautious interpretation of our findings. First, the data were derived from a single-center ICU database, which may limit the generalizability of our results. Second, this study only recorded the initial monitoring indicators within 24 h of admission and did not capture dynamic changes in LDH levels during hospitalization, which could have provided a more comprehensive understanding of their association with mortality. Furthermore, while our study demonstrated a significant relationship between baseline LDH levels and mortality, the lack of direct comparison with other biomarkers, such as lactic acid or BNP, restricts our ability to assess the relative prognostic value of LDH. Finally, as a retrospective observational study, there may be inherent measurement errors or unmeasured confounders that could affect the results. Multicenter, prospective studies are needed to further validate our findings and investigate the clinical implications of LDH as a biomarker in heart failure patients.

Conclusion

This study shows that elevated LDH levels are significantly associated with increased all-cause mortality in ICU patients with heart failure. Monitoring LDH levels may therefore be a useful part of risk assessment in these patients. Further research is needed to explore the mechanisms behind this association and evaluate potential targeted interventions.

Supplementary Information

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Supplementary Material 1: Supplementary Fig. 1: Graph of the percentage of missing variables in the MIMIC database for patients with heart failure. Supplementary Fig. 2: Standardized mean difference (SMD) of overlapping weighted before and after variables in the original cohort. Supplementary table 1: The ICD-9 and ICD-10 codes for identifying heart failure Supplementary table 2: Univariate COX regression analysis of in-hospital mortality in critically ill patients with heart failure. Supplementary table 3: The variance inflation factor for all covariates of the fully adjusted model

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Author contributions

PG, HD and PW formulated the research questions and designed the study. KW and WS carried out literature search. PG extracted clinical data from the MIMIC-IV database. XL, DX and XY conducted the data analysis. HD and PG drafted the manuscript. FN and PW critically reviewed, edited, and approved the manuscript. HD and PG finalized the manuscript based on all the authors' comments. All authors provided comments and approved the final manuscript.

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Data availability

Publicly available datasets were analyzed in this study. These datasets can be accessed at https://physionet.org/content/mimiciv/2.2/. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The database was approved for research use by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. All patient information in the database is anonymized and therefore does not require informed consent. We completed online courses and exams and gained access to the database (record ID: 58462281).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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