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The association between the MELD-XI score and 30-day mortality in ICU patients with sepsis: a retrospective cohort study

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Sepsis is a leading cause of mortality among ICU patients. Although APACHE IV and SOFA scores are widely employed for prognostic assessment, their complexity and dependence on extensive data may limit their effectiveness in early risk identification. The MELD-XI score, derived from serum total bilirubin and creatinine, offers a simple calculation method and has demonstrated strong prognostic value in liver disease, organ transplantation, and cardiovascular conditions. However, its prognostic utility in ICU patients with sepsis has not been systematically evaluated. In this study, we retrospectively analyzed 16,691 adult patients diagnosed with sepsis within 48 h of ICU admission using data from the eICU Collaborative Research Database. Through the application of a generalized additive model and a two-stage linear regression model, we identified for the first time a significant nonlinear association and a threshold effect between MELD-XI scores and 30-day all-cause mortality. The turning point was determined at a MELD-XI score of 25.74, with mortality risk increasing by 1.1% per unit below the threshold and by 5.5% per unit above it. Stratified subgroup analyses confirmed the consistency of this association across most clinical categories. These findings suggest that the MELD-XI score may serve as a simple, accessible, and complementary tool for early risk stratification and clinical decision-making in ICU patients with sepsis.

Keywords MELD-XI, Sepsis, Mortality, Threshold effect, Critical care medicine

Sepsis is the leading cause of death in ICU patients worldwide. In 2017, there were 48.9 million new cases of sepsis and 11 million sepsis-related deaths globally, representing 19.7% of all deaths worldwide[1]. Its high morbidity and mortality present significant challenges to healthcare systems. Early identification of high-risk patients is crucial in clinical practice for developing personalized treatment strategies, optimizing resource allocation, and improving patient prognosis.

The APACHE IV(Acute Physiology and Chronic Health Evaluation IV) and SOFA(Sequential Organ Failure Assessment) scores, commonly used in clinical settings, are essential tools for the prognostic assessment of sepsis[2,3]. However, their complexity and reliance on comprehensive data may result in delayed evaluation. In contrast, the MELD-XI(Model for End-Stage Liver Disease Excluding International Normalized Ratio) score[4] is calculated using serum total bilirubin and creatinine, according to the formula: $\text{MELD-XI} = 5.11 \times \ln(\text{serum total bilirubin}) + 11.76 \times \ln(\text{serum creatinine}) + 9.44$ [4,5]. Both serum total bilirubin and creatinine are strongly associated with the prognosis of patients with sepsis[6–8]. The MELD score has been widely used to assess mortality risk and guide organ transplant allocation in patients with liver disease and has demonstrated high accuracy in predicting prognosis[9,10] and mortality in conditions such as heart failure[11]. However, the relationship between MELD-XI scores and mortality in septic patients in the ICU remains insufficiently explored.

Therefore, based on data from the eICU Collaborative Research Database (eICU-CRD), this study examines the correlation between the MELD-XI score and the 30-day all-cause mortality rate in patients who developed sepsis within 48 h of ICU admission.

Methods
Data source
The data for this study were obtained from the eICU Collaborative Research Database (eICU-CRD), developed jointly by the Massachusetts Institute of Technology and Philips Healthcare[12]. This database includes clinical

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data from over 200,000 critically ill patients across 335 intensive care units in 208 hospitals in the United States, spanning from 2014 to 2015. It encompasses a wide range of variables, such as demographic information, vital signs, laboratory tests, diagnoses, treatments, and outcomes. Access to the database is granted only after completion of the Collaborative Institutional Training Initiative (CITI). The first author of this study (Jiehe Mai) obtained access to the eICU-CRD and was responsible for data extraction (certification number: 67879753). The security architecture of the eICU-CRD, independently evaluated by privacy experts (Privacert, Cambridge, Massachusetts), was certified as compliant with the Safe Harbor standard for re-identification risk (Health Insurance Portability and Accountability Act certification number: 1031219-2). Approval was waived by the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, MA, USA) for this retrospective study. Informed consent was also waived by the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, MA, USA) because only de-identified data were used. All operations followed the principles outlined in the Declaration of Helsinki and complied with the STROBE guidelines for observational studies.

Study population

All relevant data for patients diagnosed with sepsis within 48 h of ICU admission were retrieved from the eICU Collaborative Research Database (eICU-CRD) using Structured Query Language (SQL). Inclusion criteria consisted of adult patients (age > 18 years) diagnosed with sepsis within 48 h of ICU admission. Sepsis was defined as suspected or confirmed infection combined with an acute increase in the Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points[13]. The site of infection was identified using International Classification of Diseases, Ninth Revision (ICD-9) codes recorded in the eICU-CRD. Exclusion criteria included (1) Age ≤ 18 years, (2) Not the first ICU admission, (3) Length of hospital stay or ICU stay < 48 h, (4) Non-septic patients, (5) Patients diagnosed with sepsis more than 48 h after ICU admission, (6) Missing data on serum total bilirubin and creatinine within the time window from − 6 to 48 h after ICU admission. The flow chart of the study is shown in Fig. 1.

Variables

Baseline demographic information, including age and sex, was obtained from the patient form. Records of dialysis treatment in the medical history were used to identify patients with prior renal replacement therapy. Comorbidities—including congestive heart failure, cardiac arrhythmias, chronic lung disease, severe liver disease, renal failure, malignancy, and metastatic solid tumors—were extracted based on the APACHE IV scoring system. Septic shock was identified using diagnostic records. Severity of illness was assessed using the Glasgow Coma Scale (GCS), APACHE IV score, and SOFA score. Laboratory parameters included the peak values of total bilirubin, serum creatinine, and lactate levels within 48 h of ICU admission.

Scoring formula

The MELD-XI score was calculated using the following formula:

MELD-XI = 5.11 × ln (serum total bilirubin) + 11.76 × ln (serum creatinine) + 9.44[4,5]. According to the United Network for Organ Sharing (UNOS) modification guidelines[14], the lower limit for serum creatinine was set at 1.0 mg/dL and the upper limit at 4.0 mg/dL. Serum creatinine values for patients receiving preoperative dialysis were uniformly set at 4.0 mg/dL to ensure stability and comparability in MELD-XI scoring.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. Patients were stratified into tertiles based on MELD-XI scores. One-way analysis of variance (ANOVA) was used to compare continuous variables across groups, and the chi-square test was applied for categorical variables. To evaluate the potential nonlinear relationship between MELD-XI score and 30-day all-cause mortality in ICU patients with sepsis, a generalized additive model (GAM) with a logistic regression link function was employed. The smoothing term was fitted using penalized cubic regression splines. This method avoids the need for a predefined functional form and enables flexible modeling of complex dose–response relationships. Confounding variables were selected based on prior association with mortality or a ≥ 10% change in effect estimate[15]. Adjusted covariates included ethnicity, age, septic shock, site of infection (lung, urinary tract, skin/bone/joint), history of dialysis, cardiac arrhythmia, severe liver disease, renal failure, malignancy, metastatic solid tumors, as well as APACHE IV score, SOFA score, GCS score, and lactate level. To further investigate potential inflection points in the relationship between MELD-XI score and mortality risk, a two-piecewise linear regression model was applied. The optimal turning point was determined using an iterative search method based on likelihood maximization. The log-likelihood ratio test (LRT) was used to compare the goodness-of-fit between a unilinear model and the segmented model. Odds ratios (ORs) for MELD-XI score below and above the inflection point were calculated separately, and 95% confidence intervals (CIs) were estimated using bootstrap resampling methods to assess effect differences across score intervals[16]. Stratified analyses were performed to evaluate the robustness of the findings. All statistical analyses were conducted using R software (version 4.2.0) and EmpowerStats (X&Y Solutions, Inc., Boston, MA).

To address missing values in key covariates, we used the predictive mean matching (PMM) algorithm from the mice package in R to perform five imputations for lactate (27.3%), APACHE IV (9.3%), and GCS (16.7%), all with missing rates below 30%. The pooled results were used for subsequent analyses to minimize potential bias.
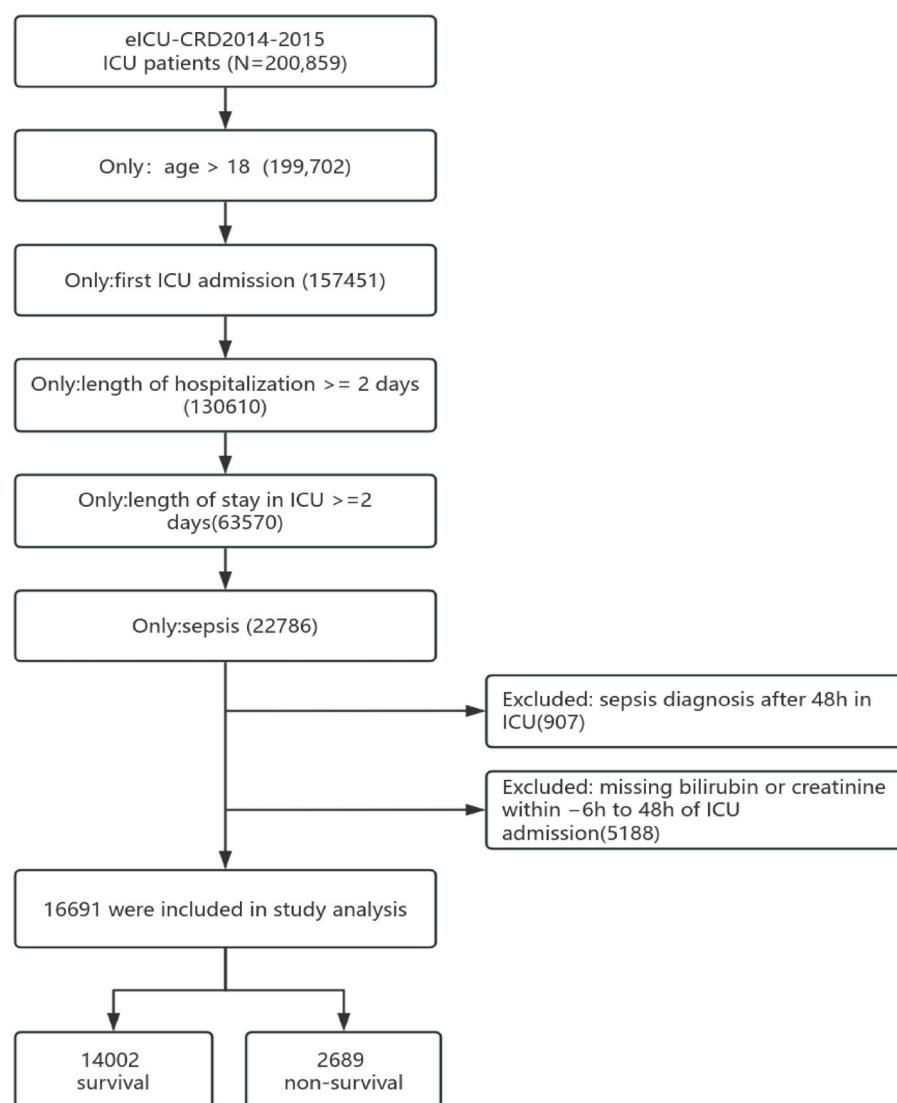
Fig. 1. Flow chart of study population.eICU-CRD:eICU Collaborative Research Database; ICU: intensive care unit.

Results
Basic characteristics
In this study, 16,691 adult patients with sepsis admitted to the ICU were included and categorized into three groups based on MELD-XI score tertiles: low (9.4–12.5), medium (12.5–21.5), and high (21.5–46) score ranges. The overall MELD-XI score was 17.69 ± 7.16. Statistically significant differences were observed among the three groups in terms of demographic characteristics, laboratory parameters, site of infection, disease severity, comorbidities, and 30-day mortality (all $P < 0.001$).

The high MELD-XI group had a greater proportion of male patients, significantly higher APACHE IV and SOFA scores, and lower Glasgow Coma Scale (GCS) scores. Laboratory tests revealed significantly elevated levels of total bilirubin, serum creatinine, and lactate in this group compared to the medium and low MELD-XI groups. In terms of infection site, abdominal cavity infections and septic shock were more common in the high MELD-XI group. Comorbidity analysis showed the highest prevalence of heart failure, severe liver disease, and renal failure in this group. Additionally, patients with a history of dialysis were only observed in the high MELD-XI group. The 30-day mortality rate was 20.27% in the high MELD-XI group, significantly higher than in the medium (16.69%) and low (11.32%) groups ($P < 0.001$). Detailed group characteristics are presented in Table 1.

Unadjusted association between baseline variablesand 30-day mortality
Each one-point increase in the MELD-XI score was associated with a 4% increase in the 30-day risk of death (OR = 1.04, 95% CI: 1.04–1.05, $P < 0.0001$). Using the lowest tertile group as the reference, the risk of death was higher by 57% in the middle tertile group (OR = 1.57, 95% CI: 1.41–1.75) and by 99% in the highest tertile group (OR = 1.99, 95% CI: 1.79–2.21), with all differences reaching statistical significance ($P < 0.0001$). Older age, elevated total bilirubin, serum creatinine, and lactate levels, as well as higher APACHE IV and SOFA scores,

Parameters	%(Number) missing	Overall (9.4–46) 16,691	MELD-XI			P-value
			Low (9.4–12.5) 5520	Middle (12.5–21.5) 5586	High (21.5–46) 5585	
Demographics						
Ethnicity	131(0.78%)		< 0.001			
African American	0	1770 (10.69%)	436 (7.97%)	535 (9.66%)	799 (14.39%)	
Asian	0	284 (1.71%)	100 (1.83%)	96 (1.73%)	88 (1.59%)	
Caucasian	0	12,829 (77.47%)	4374 (79.98%)	4373 (78.95%)	4082 (73.52%)	
Hispanic	0	728 (4.40%)	233 (4.26%)	232 (4.19%)	263 (4.74%)	
Native American	0	134 (0.81%)	37 (0.68%)	29 (0.52%)	68 (1.23%)	
Other/Unknown	0	815 (4.92%)	289 (5.28%)	274 (4.95%)	252 (4.54%)	
Gender	3(0.02%)					
Female	0		2955 (53.54%)	2532 (45.34%)	2372 (42.47%)	< 0.001
Male	0		2564 (46.46%)	3052 (54.66%)	3213 (57.53%)	
Age	0	65.08 ± 15.96	62.93 ± 16.83	67.69 ± 15.64	64.61 ± 15.01	< 0.001
Laboratory data						
Total Bilirubin	0	1.71 ± 2.63	1.05 ± 0.14	1.47 ± 1.08	2.59 ± 4.26	< 0.001
Creatinine	0	1.97 ± 1.08	1.04 ± 0.08	1.70 ± 0.45	3.17 ± 0.96	< 0.001
Lactate	4520(27.3%)	3.33 ± 3.08	2.48 ± 2.02	3.38 ± 2.83	4.01 ± 3.80	< 0.001
Infection						
Pulmonary Infection	0	6967 (41.74%)	2835 (51.36%)	2343 (41.94%)	1789 (32.03%)	< 0.001
renal/UrinaryTract Infection	0	1676 (10.04%)	537 (9.73%)	601 (10.76%)	538 (9.63%)	0.090
Skin/Bone/ joint Infection	0	1129 (6.76%)	340 (6.16%)	380 (6.80%)	409 (7.32%)	0.050
Gastrointestinal/ intra0abdominal Infection	0	1043 (6.25%)	261 (4.73%)	355 (6.36%)	427 (7.65%)	< 0.001
Septic shock	0	7368 (44.14%)	2112 (38.26%)	2475 (44.31%)	2781 (49.79%)	< 0.001
Severity of illness						
APACHE IV	1558(9.3%)	73.12 ± 27.32	62.70 ± 23.60	73.91 ± 26.01	82.37 ± 28.40	< 0.001
SOFA	0	8.06 ± 3.59	6.80 ± 3.04	7.89 ± 3.39	9.46 ± 3.77	< 0.001
GCS	2794(16.7%)	9.59 ± 4.37	9.80 ± 4.24	9.67 ± 4.40	9.29 ± 4.46	< 0.001
Comorbidities						
Congestive heart failure	0	3165 (18.96%)	737 (13.35%)	1201 (21.50%)	1227 (21.97%)	< 0.001
Cardiac arrhythmias	0	3405 (20.40%)	1009 (18.28%)	1290 (23.09%)	1106 (19.80%)	< 0.001
Severe liver disease	0	462 (2.77%)	43 (0.78%)	134 (2.40%)	285 (5.10%)	< 0.001
Renal failure	0	2540 (15.22%)	176 (3.19%)	724 (12.96%)	1640 (29.36%)	< 0.001
Malignant cancer	0	2483 (14.88%)	845 (15.31%)	886 (15.86%)	752 (13.47%)	< 0.001
Metastatic solid tumor	0	512 (3.07%)	192 (3.48%)	177 (3.17%)	143 (2.56%)	0.017
History of dialysis	0	964 (5.78%)	0 (0.00%)	0 (0.00%)	964 (17.26%)	< 0.001
Mortality 30						
0	0	14,002 (83.89%)	4895 (88.68%)	4654 (83.32%)	4453 (79.73%)	< 0.001
1	0	2689 (16.11%)	625 (11.32%)	932 (16.69%)	1132 (20.27%)	

Table 1. The baseline characteristics and 30-day mortality according to the tertiles of the MELD-XI score (n = 16,691). Data are expressed as the mean ± SD, median (interquartile range), or percentage. Abbreviations: GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MELD-XI, Model for End-Stage Liver Disease Excluding INR.

were associated with an increased risk of 30-day mortality. In contrast, higher GCS scores were significantly associated with a reduced risk of death ($P < 0.0001$). Pulmonary infections and septic shock were also linked to a higher risk of mortality. In contrast, skin/bone/joint infections (OR = 0.74, $P = 0.0012$) and a history of dialysis (OR = 0.71, $P = 0.0006$) were associated with lower mortality risk.

Comorbidities such as severe liver disease, malignant tumors, metastatic solid tumors, cardiac arrhythmias, and renal failure were significantly associated with an increased risk of death. Sex and most infection sites were not significantly related to mortality risk. Detailed results are presented in Table 2.

Multivariable logistic regression analyses in different adjustment models
Further multivariate analysis demonstrated a significant positive association between the MELD-XI score and 30-day all-cause mortality (Table 3). In the fully adjusted model, for every 1-point increase in the MELD-XI score, the risk of 30-day all-cause mortality increased by 2% (OR = 1.02, 95% CI: 1.01–1.02; $P = 0.00019$).

Expoure	Statistics	Odds ratio (95% CI)	P-value
MELD-XI	17.69 ± 7.16	1.04 (1.04, 1.05)	**< 0.0001**
MELD-XI tertile			
Low	5520 (33.07%)	1.0	
Middle	5586 (33.47%)	1.57 (1.41, 1.75)	**< 0.0001**
High	5585 (33.46%)	1.99 (1.79, 2.21)	**< 0.0001**
Ethnicity			
African American	1770 (10.69%)	1.0	
Asian	284 (1.71%)	1.43 (1.04, 1.96)	**0.0261**
Caucasian	12,829 (77.47%)	1.09 (0.95, 1.25)	0.2414
Hispanic	728 (4.40%)	1.08 (0.85, 1.37)	0.5257
Native American	134 (0.81%)	1.28 (0.81, 2.01)	0.2864
Other/Unknown	815 (4.92%)	0.90 (0.71, 1.14)	0.3752
Gender			
Female	7859 (47.09%)	1.0	
Male	8829 (52.91%)	1.07 (0.98, 1.16)	0.1152
Age	65.0 ± 15.96	1.02 (1.02, 1.02)	**< 0.0001**
Total Bilirubin	1.71 ± 2.63	1.08 (1.06, 1.09)	**< 0.0001**
Creatinine	1.97 ± 1.08	1.21 (1.17, 1.26)	**< 0.0001**
Lactate	3.33 ± 3.08	1.15 (1.13, 1.16)	**< 0.0001**
Pulmonary Infection	6967 (41.74%)	1.18 (1.09, 1.28)	**< 0.0001**
Renal/urinary tract infection	1676 (10.04%)	0.88 (0.76, 1.01)	0.0685
Skin/Bone/joint Infection	1129 (6.76%)	0.74 (0.62, 0.89)	**0.0012**
Gastrointestinal/Intra-abdominal Infection	1043 (6.25%)	1.12 (0.95, 1.33)	0.1650
Septic shock	7368 (44.14%)	1.30 (1.19, 1.41)	**< 0.0001**
APACHE IV	73.12 ± 27.32	1.03 (1.02, 1.03)	**< 0.00001**
SOFA	8.06 ± 3.59	1.24 (1.23, 1.26)	**< 0.00001**
GCS	9.59 ± 4.37	0.81 (0.80, 0.82)	**< 0.00001**
Congestive heart failure	3165 (18.96%)	1.09 (0.98, 1.21)	0.0949
Cardiac arrhythmias	3405 (20.40%)	1.42 (1.29, 1.57)	**< 0.0001**
Severe liver disease	462 (2.77%)	2.12 (1.72, 2.60)	**< 0.0001**
Renal failure	2540 (15.22%)	1.21 (1.08, 1.35)	**0.0007**
Malignant cancer	2483 (14.88%)	1.59 (1.43, 1.77)	**< 0.0001**
Metastatic solid tumor	512 (3.07%)	2.57 (2.13, 3.11)	**< 0.0001**
History of dialysis	964 (5.78%)	0.71 (0.58, 0.86)	**0.0006**

Table 2. The unadjusted association between baseline variables and 30-day mortality (n = 16,691) Abbreviations: GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MELD-XI, Model for End-Stage Liver Disease Excluding INR. Values in bold indicate statistical significance at $P < 0.05$.

Exposure	Non-adjusted	Adjust I	Adjust II	Adjust III
MELD-XI	1.04(1.04, 1.05) < 0.00001	1.05(1.04,1.06) < 0.00001	1.02 (1.01, 1.03) < 0.00001	1.02 (1.01, 1.02) 0.00019
MELD-XI tertile				
9.4–12.5	1.0	1.0	1.0	1.0
12.5–21.5	1.57(1.41, 1.75) < 0.00001	1.47(1.31,1.64) < 0.00001	1.17 (1.03, 1.32) 0.01319	1.13 (1.00, 1.28) 0.04348
21.5–46	1.99 (1.79,2.21) < 0.00001	2.02(1.81,2.26) < 0.00001	1.29 (1.13, 1.49) 0.00021	1.23 (1.07, 1.41) 0.00354

Table 3. Multivariable logistic regression analyses were performed to assess the association between MELD-XI score and 30-day mortality across different models. Abbreviations: MELD-XI, Model for End-Stage Liver Disease Excluding INR. Data are presented as OR (95% CI), P-value. Non-adjusted model (n = 16,691): no covariates adjusted. Adjusted model I (n = 16,688): adjusted for ethnicity, gender, age, septic shock, pulmonary infection, urinary tract infection, and skin/bone/joint infection. Adjusted model II (n = 16,558): further adjusted for history of dialysis, cardiac arrhythmias, severe liver disease, renal failure, malignant tumor, metastatic cancer, APACHE IV, SOFA, and GCS. Adjusted model III (n = 16,558): further adjusted for lactate. Model II and model III based on imputed data for APACHE IV, GCS, and lactate.
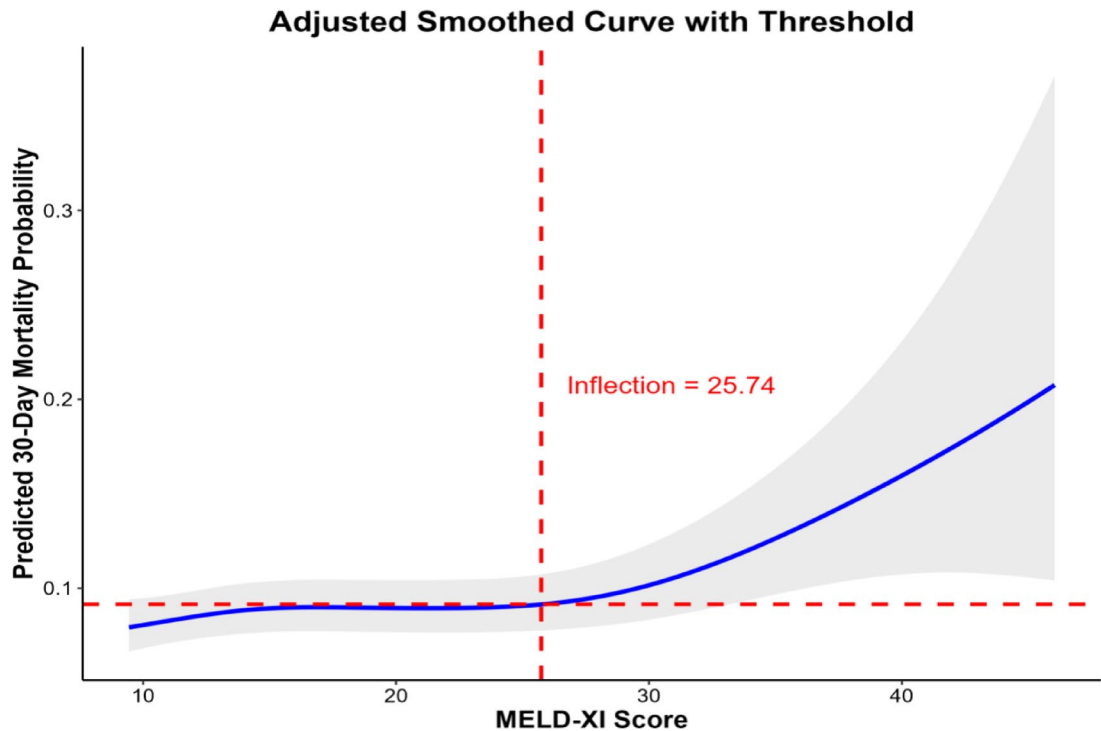
Fig. 2. Associations between the MELD-XI score and 30-day all-cause mortality in ICU patients with sepsis.

Models	Odds ratio (95% CI)	*P*-value
Model I		
One-line effect	1.01(1.00, 1.02)	0.014
Model II		
Turning point(K)	25.74	
MELD-XI score < K	1.01 (0.99, 1.02)	0.389
MELD-XI score > K	1.05(1.02, 1.08)	0.003
Difference in effects (segment 2 vs. segment 1)	1.04 (1.01, 1.08)	0.023
LRT logarithm likelihood ratio test		0.007

Table 4. Threshold effect analysis of the MELD-XI score and 30-day mortality. Data in the table: β(95%CI) *P*-value/OR (95%CI) *P*-value; CI: confidence interval. LRT: logarithm likelihood ratio test. MELD-XI: Model for End-Stage Liver Disease Excluding INR *P* < 0.05 indicates that Model II is significantly different from Model I. The 95 confidence interval of the folding point(22.82, 25.74) The model was adjusted for ethnicity, gender, age, septic shock, pulmonary infection, renal/urinary tract infection, skin/bone/joint infection, history of dialysis, cardiac arrhythmias, severe liver disease, renal failure, malignant cancer, metastatic solid tumor, APACHE IV score, SOFA score, and GCS score. Abbreviations: MELD-XI, Model for End-Stage Liver Disease Excluding INR.

Compared to the lowest MELD-XI tertile (T1), the 30-day all-cause mortality rate in the highest tertile was 23% higher (OR = 1.23, 95% CI: 1.07–1.41; *P* = 0.00354), while the middle tertile was associated with a 13% higher mortality rate (OR = 1.13, 95% CI: 1.00–1.28; *P* = 0.04348). The trend tests across all models were statistically significant (all *P*-values < 0.01), emphasizing the strong and consistent positive association between MELD-XI scores and 30-day all-cause mortality.

Identification of nonlinear relationships and threshold effect analysis

Figure 2 shows a nonlinear relationship between MELD-XI score and 30-day mortality in ICU patients with sepsis (*P* for nonlinearity < 0.001). The inflection point for MELD-XI was 25.74. This difference was confirmed to be statistically significant by the likelihood ratio test of the two-piecewise linear regression model (*P* = 0.007, Table 4). Specifically, when MELD-XI < 25.74, the association with mortality was not statistically significant (OR = 1.005, 95% CI: 0.993–1.018; *P* = 0.389). However, when MELD-XI ≥ 25.74, each 1-point increase in MELD-

XI was associated with a 4.8% higher risk of 30-day mortality (OR = 1.048, 95% CI: 1.016–1.081; *P* = 0.00287), indicating that 25.74 may serve as a mortality risk threshold, above which the risk increases significantly.

A nonlinear association between the MELD-XI score and 30-day mortality was identified using a generalized additive model (GAM). The solid blue line represents the fitted smooth curve, while the shaded grey area indicates the 95% confidence intervals. MELD-XI was used as the independent variable. The model was adjusted for ethnicity, gender, age, septic shock, pulmonary infection, renal/urinary tract infection, skin/bone/joint infection, history of dialysis, cardiac arrhythmias, severe liver disease, renal failure, malignant cancer, metastatic solid tumor, Lactate, APACHE IV score, SOFA score, and GCS score. Abbreviations: MELD-XI, Model for End-Stage Liver Disease excluding INR.

Stratified analysis

To evaluate the robustness of the association between the MELD-XI score and 30-day all-cause mortality, a stratified subgroup analysis was performed using multiple imputation data (Fig. 3). The results demonstrated a consistent positive association across most subgroups, with odds ratios (ORs) ranging from approximately 1.02 to 1.13, supporting the score's robust prognostic value across diverse ICU populations. Notably, the association was most pronounced in patients with a history of dialysis (OR = 1.13, 95% CI: 1.07–1.20), substantially higher than that in patients without dialysis (OR = 1.05), indicating that the MELD-XI score may have increased predictive power in individuals with impaired renal function. Significant associations were also observed in patients with comorbid cardiac arrhythmias (OR = 1.04), severe liver disease (OR = 1.06), renal failure (OR = 1.02), malignant cancer (OR = 1.05), and metastatic solid tumors (OR = 1.04), all with P < 0.05. Subgroup analysis by age revealed stronger associations in patients younger than 65 years (OR = 1.06) compared to those aged 65 or older (OR = 1.03). Similarly, patients with higher disease severity, as indicated by elevated APACHE IV (≥ 81: OR = 1.03) and SOFA scores (≥ 9: OR = 1.03), showed stronger associations than those with lower scores.

Discussion

In this retrospective cohort study, we included 16,691 patients diagnosed with sepsis within 48 h of ICU admission using data from the eICU database to evaluate the association between MELD-XI score and 30-day all-cause mortality. The results demonstrated that MELD-XI was an independent predictor of 30-day mortality in this population, with a significant nonlinear relationship and a threshold effect. Higher MELD-XI scores were significantly associated with increased mortality risk, and subgroup analyses further confirmed the robustness of these findings. This evidence supports the potential utility of the MELD-XI score in early risk stratification and clinical management of sepsis in the ICU.

In sepsis, the liver, as a crucial metabolic and immune organ, is vulnerable to injury from inflammatory mediators, pathogens, and toxins, which can lead to dysfunction or even failure, thereby significantly increasing mortality risk, with rates reported as high as 38.2%–68%[17]. Serum total bilirubin, an important biochemical indicator of liver function, has also been shown to correlate closely with mortality in sepsis[6,7]. Additionally, acute kidney injury (AKI) is a common complication, associated with a hospital mortality rate of 9.1%[18], and patients requiring dialysis face a mortality rate of up to 43.6%[19]. The MELD-XI score, which is calculated based on serum bilirubin and creatinine levels, is highly valuable for early risk stratification in sepsis patients[20]. Compared with APACHE IV and SOFA scores that depend on multiple organ parameters and complex calculations[2,3], MELD-XI relies on only two routine laboratory indicators (total bilirubin and creatinine), making it more suitable for rapid risk assessment in critically ill patients, especially in clinical environments with limited data or time constraints, where it offers greater practicality[21]. Furthermore, our results indicate that lactic acid plays a partial mediating role in the association between MELD-XI and 30-day mortality, with approximately 19.6% of the total effect attributable to the lactate pathway. This finding supports the hypothesis that liver and kidney dysfunction in sepsis can lead to metabolic disturbances and exacerbate disease severity. Specifically, the liver and kidney impairment reflected by the MELD-XI score may elevate lactic acid levels by impairing its metabolism and clearance, thereby increasing the mortality risk of affected patients.

In this study, we identified a significant nonlinear association between the MELD-XI score and 30-day all-cause mortality in ICU patients with sepsis, indicating a distinct threshold effect. The risk of death increased gradually at scores below 25.74 but rose sharply when the MELD-XI score exceeded this threshold. This inflection point may represent a critical threshold beyond which hepatic and renal dysfunction overwhelm the body's compensatory mechanisms, resulting in the loss of internal homeostatic regulation. Hepatic and renal functions play vital roles in metabolic regulation and systemic homeostasis. Sepsis, characterized by a systemic inflammatory response to infection, often involves elevated inflammatory cytokines such as TNF-α, IL-6, and IL-1β[22,23]. Liver dysfunction can impair ammonia metabolism and mitochondrial activity, amplifying the inflammatory cascade[24]. Simultaneously, renal insufficiency contributes to toxin accumulation and electrolyte imbalance[25]. Recent studies have highlighted the important pathophysiological role of the liver-kidney axis in sepsis, where bidirectional dysfunction may exacerbate systemic inflammation and organ failure. Specifically, hepatic impairment may hinder the clearance of gut-derived toxins and inflammatory mediators, placing additional burden on renal excretory pathways and forming a vicious cycle of multiorgan dysfunction[26,27]. This feedback loop may help explain the sharp rise in mortality observed beyond the MELD-XI inflection point (≥ 25.74), as it likely reflects the exhaustion of hepatic-renal compensatory reserve. However, the magnitude of this threshold effect may also be influenced by methodological factors, such as the fixed creatinine value assigned to dialysis patients under the MELD-XI scoring criteria, which could potentially lead to bias in the observed outcomes.

Therefore, the MELD-XI score not only reflects the degree of organ dysfunction but may also serve as a potential alternative indicator of hepatorenal dysfunction in critically ill patients with sepsis. Based on the inflection point identified in this study (25.74), patients with higher MELD-XI scores should warrant heightened
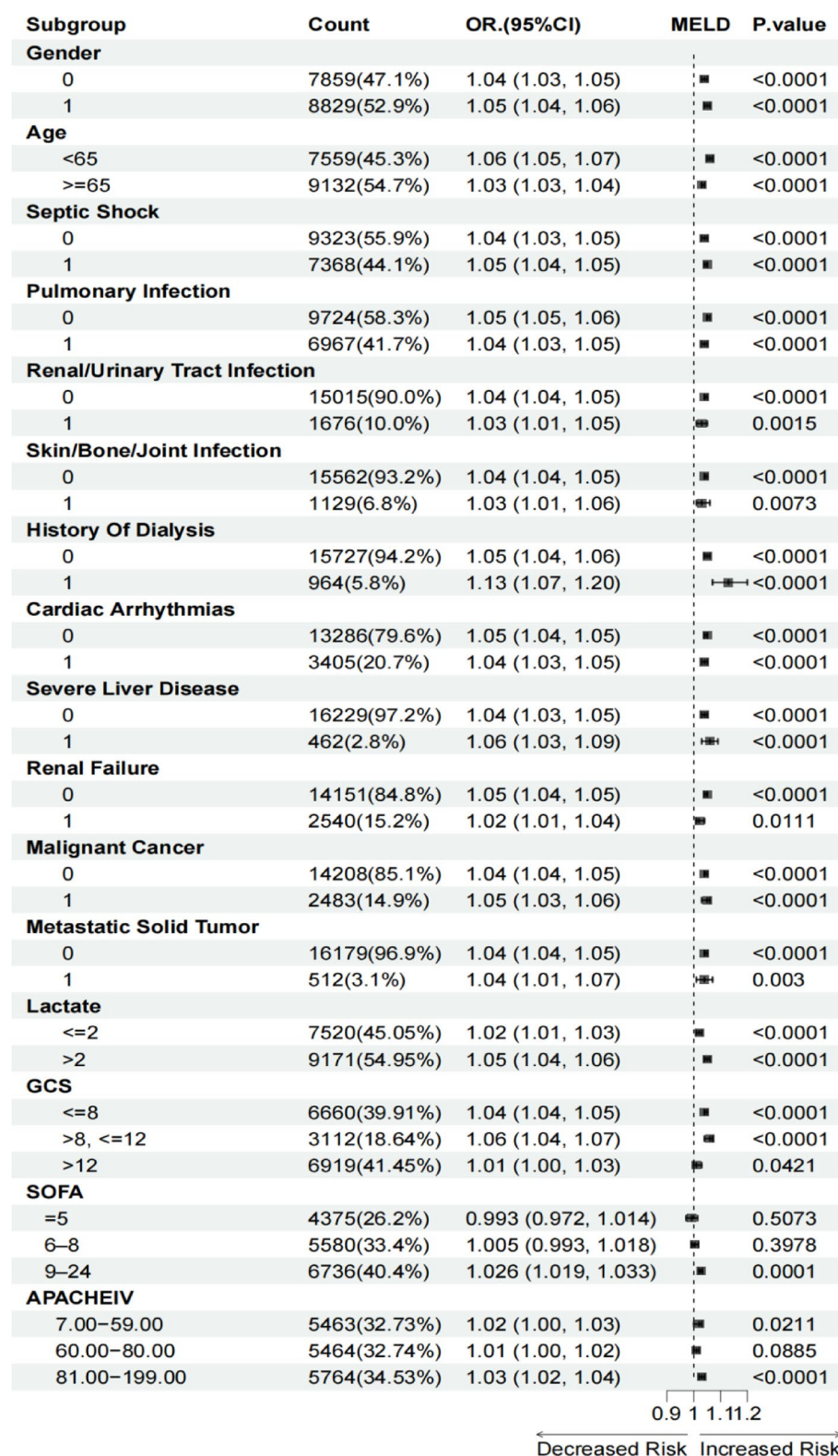
Subgroup	Count	OR.(95%CI)	MELD	P.value
Gender				
0	7859(47.1%)	1.04 (1.03, 1.05)		<0.0001
1	8829(52.9%)	1.05 (1.04, 1.06)		<0.0001
Age				
<65	7559(45.3%)	1.06 (1.05, 1.07)		<0.0001
>=65	9132(54.7%)	1.03 (1.03, 1.04)		<0.0001
Septic Shock				
0	9323(55.9%)	1.04 (1.03, 1.05)		<0.0001
1	7368(44.1%)	1.05 (1.04, 1.05)		<0.0001
Pulmonary Infection				
0	9724(58.3%)	1.05 (1.05, 1.06)		<0.0001
1	6967(41.7%)	1.04 (1.03, 1.05)		<0.0001
Renal/Urinary Tract Infection				
0	15015(90.0%)	1.04 (1.04, 1.05)		<0.0001
1	1676(10.0%)	1.03 (1.01, 1.05)		0.0015
Skin/Bone/Joint Infection				
0	15562(93.2%)	1.04 (1.04, 1.05)		<0.0001
1	1129(6.8%)	1.03 (1.01, 1.06)		0.0073
History Of Dialysis				
0	15727(94.2%)	1.05 (1.04, 1.06)		<0.0001
1	964(5.8%)	1.13 (1.07, 1.20)		<0.0001
Cardiac Arrhythmias				
0	13286(79.6%)	1.05 (1.04, 1.05)		<0.0001
1	3405(20.7%)	1.04 (1.03, 1.05)		<0.0001
Severe Liver Disease				
0	16229(97.2%)	1.04 (1.03, 1.05)		<0.0001
1	462(2.8%)	1.06 (1.03, 1.09)		<0.0001
Renal Failure				
0	14151(84.8%)	1.05 (1.04, 1.05)		<0.0001
1	2540(15.2%)	1.02 (1.01, 1.04)		0.0111
Malignant Cancer				
0	14208(85.1%)	1.04 (1.04, 1.05)		<0.0001
1	2483(14.9%)	1.05 (1.03, 1.06)		<0.0001
Metastatic Solid Tumor				
0	16179(96.9%)	1.04 (1.04, 1.05)		<0.0001
1	512(3.1%)	1.04 (1.01, 1.07)		0.003
Lactate				
<=2	7520(45.05%)	1.02 (1.01, 1.03)		<0.0001
>2	9171(54.95%)	1.05 (1.04, 1.06)		<0.0001
GCS				
<=8	6660(39.91%)	1.04 (1.04, 1.05)		<0.0001
>8, <=12	3112(18.64%)	1.06 (1.04, 1.07)		<0.0001
>12	6919(41.45%)	1.01 (1.00, 1.03)		0.0421
SOFA				
=5	4375(26.2%)	0.993 (0.972, 1.014)		0.5073
6–8	5580(33.4%)	1.005 (0.993, 1.018)		0.3978
9–24	6736(40.4%)	1.026 (1.019, 1.033)		0.0001
APACHEIV				
7.00−59.00	5463(32.73%)	1.02 (1.00, 1.03)		0.0211
60.00−80.00	5464(32.74%)	1.01 (1.00, 1.02)		0.0885
81.00−199.00	5764(34.53%)	1.03 (1.02, 1.04)		<0.0001

0.9 1 1.11.2

Decreased Risk ← | → Increased Risk

Fig. 3. Subgroup analysis of the association between MELD-XI score and 30-day mortality in ICU patients with sepsis. Multivariable logistic regression models were used to assess the association between MELD-XI score and mortality risk across clinical subgroups. Odds ratios (ORs) and their 95% confidence intervals (CIs) are presented. The x-axis is plotted on a logarithmic scale; the vertical dashed line represents the reference value of OR = 1, with points to the right indicating increased mortality risk. Abbreviations: GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; MELD-XI, Model for End-Stage Liver Disease Excluding INR.

clinical attention. These patients should be evaluated in the context of their overall condition, with priority given to continuous and dynamic monitoring. At an appropriate time, liver-protective treatments (e.g., artificial liver support systems) or renal replacement therapy (RRT) should be considered to improve prognosis and guide resource allocation[28,29]. Additionally, future studies should conduct mechanistic research to further explore the biological plausibility of this threshold and provide a foundation for optimizing early intervention strategies. Although this threshold appears biologically plausible and statistically significant, its clinical applicability should be further validated in prospective, multicenter studies to ensure its feasibility and effectiveness in real-world clinical decision-making.

Strengths and limitations

This study was conducted using the Electronic Intensive Care Unit Collaborative Research Database, a large-scale, multicenter intensive care dataset comprising 16,691 ICU patients with sepsis, which enhances the reliability and statistical power of our findings. Although previous studies have examined the prognostic value of the MELD-XI score, our analysis identified a nonlinear association between the MELD-XI score and mortality and further revealed a specific turning point, offering a valuable reference for future research on sepsis risk stratification and clinical decision-making. Nonetheless, several limitations should be acknowledged. First, as a retrospective analysis, the study is inherently subject to residual confounding, despite adjustment for multiple covariates. Second, although multiple imputation was applied to address missing data and reduce potential bias, the possibility of residual selection bias cannot be entirely excluded. Third, the data were derived from U.S. community hospitals, where illness severity was generally mild; therefore, the generalizability of our findings to specialized intensive care units or non-Western populations with different ethnic backgrounds and healthcare systems may be limited and requires further external validation. Fourth, for patients with a history of dialysis, we assigned a fixed serum creatinine value of 4.0 mg/dL in accordance with MELD-XI scoring criteria to ensure consistency and comparability. This approach may have artificially inflated MELD-XI scores in this subgroup, potentially contributing to the paradoxical finding of lower unadjusted mortality and the strong association observed in the subgroup analysis due to misclassification bias.

Building on these findings, future research may focus on the following areas: First, the prognostic value of the MELD-XI score in sepsis should be validated in independent, prospective cohorts to enhance its external validity. Second, the MELD-XI score could be integrated with existing prognostic systems—such as SOFA, qSOFA, and lactate levels—to develop a composite prognostic model with improved predictive accuracy and clinical applicability. Finally, given the significantly increased risk of mortality observed when the MELD-XI score exceeds 25.74, future intervention trials could assess whether risk stratification based on this threshold can guide timely and targeted clinical management strategies, ultimately improving patient outcomes.

Conclusion

This study found a nonlinear relationship and threshold effect between the MELD-XI score and 30-day mortality in ICU patients with sepsis. When the MELD-XI score exceeds 25.74, the risk of death rises significantly. As a simple and practical scoring tool, MELD-XI may aid in early risk assessment in clinical settings. Further prospective studies are needed to validate this threshold and assess its utility in guiding treatment decisions.

Data availability

The data that support the findings of this study are available from the eICU Collaborative Research Database, which is publicly accessible at https://eicu-crd.mit.edu/. Access to the database requires completion of a data use agreement and relevant training.

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Author contributions

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

Ethical approval was waived by the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, MA, USA) for this retrospective study due to the lack of direct patient intervention and the use of a security schema certified to meet the HIPAA Safe Harbor standard for re-identification risk by an independent privacy expert (Privacert, Cambridge, MA; Certification No. 1031219-2). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to all relevant institutional guidelines.

Consent for publication

Not applicable.

Informed consent

The requirement for informed consent was waived by the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, MA, USA) because only de-identified data were used.

Clinical trial number

Not applicable.

Additional information

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