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Effect of timing of intubation on clinical outcomes of patients with septic shock: a retrospective cohort study

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Evidence-based data regarding the timing of the application of invasive mechanical ventilation among adults with septic shock is insufficient. The guidelines fail to provide clear advice about the optimal time to initiate this support. Consequently, we aimed to investigate whether early intubation could improve survival rates in septic shock patients. We conducted a retrospective analysis of the MIMIC-IV database to evaluate the effectiveness of early intubation on mortality in a cohort of septic shock patients. Adults diagnosed with septic shock, according to the Sepsis-3 definition, were included. They were categorized into an early intubation group (first 8 h after vasopressor initiation) and a non-early intubation group (unexposed). A propensity score matching (PSM) analysis was used to balance the baseline characteristics between the two groups. The primary outcomes were 30-day and 90-day all-cause mortality rates. In addition, we employed the restricted cubic spline to analyze the potential non-linear relationship between the timing of intubation and 30-day or 90-day all-cause mortality. A total of 6864 adult patients, of whom 2048 were intubated in the first 8 h, were evaluated in the final cohort. Following a 1:1 PSM procedure, 2786 patients were successfully paired. At 30 days, 288 of 1393 patients (20.7%) in the early intubation group and 381 of 1393 patients (27.4%) in the non-early intubation group had died (hazard ratio [HR] 0.717; 95% confidence interval [CI] 0.616–0.836; $p < 0.001$). Similarly, the results also showed that early intubation was associated with a lower 90 day all-cause mortality rate (HR 0.761; 95% CI 0.663–0.874; $p < 0.001$). Furthermore, ICU and hospital lengths of stay were significantly different between the groups (3.6 [1.9, 7.1] vs. 2.3 [1.3, 4.3]; $p < 0.001$ and 8.9 [5.4, 15.1] vs. 7.2 [4.5, 12.0]; $p < 0.001$). In the subgroup analysis, we further confirmed the robustness of our findings. Additionally, we found that the timing of intubation is inversely U-shaped correlated to the 30 day all-cause mortality rate. Among adult patients with septic shock, the early initiation of invasive mechanical ventilation could improve clinical outcomes. The timing of intubation demonstrated an inverse U-shaped association with the 30 day all-cause mortality rate, with the peak risk of death occurring at 50.5 h after septic shock.

Keywords Septic shock, MIMIC IV, Timing of intubation, Propensity score-matched, Clinical outcomes

Abbreviations

MIMIC	Medical information mart in intensive care
PSM	Propensity score matching
HR	Hazard ratio
CI	Confidence interval
ICU	Intensive care unit
VAP	Ventilator-associated pneumonia
SCC	Surviving sepsis campaign
ARDS	Acute respiratory distress syndrome
SQL	Structured query language
BIDMC	Beth Israel deaconess medical center
IRB	Institutional review board
MIT	Massachusetts institute of technology

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SOFA	Sequential organ failure assessment
MAP	Mean arterial pressure
CRRT	Continuous renal replacement therapy
CHF	Congestive heart failure
MI	Myocardial infarction
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease
CCI	Charlson comorbidity index
SAPS	Simplified acute physiology score
GCS	Glasgow coma scale
IQR	Interquartile range
SMD	Standardized mean difference
RCS	Restricted cubic spline
PaO2/FiO2	Arterial oxygen partial pressure ratio to fractional inspired oxygen
AI	Artificial intelligence

Invasive mechanical ventilation is a lifesaving organ support for critically ill patients in the intensive care unit (ICU). It is often one of the main reasons why patients require intensive care. Approximately 20 million ICU patients receive invasive mechanical ventilation annually, underscoring its critical role[1]. However, invasive mechanical ventilation also carries serious risks, such as lung injury, ventilator-associated pneumonia (VAP), diaphragmatic dysfunction, delirium or neurocognitive disorders, ICU-acquired weakness due to sedation and immobility, and laryngeal injury[2–4]. In comparison with patients who are not intubated, patients who require invasive mechanical ventilation often have a higher risk of death. However, this increased risk may reflect significant differences in the severity of diseases.

Septic shock, a severe subtype of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality in critically ill patients, presents a significant challenge to ICU physicians[5]. Invasive mechanical ventilation is often used in this population, especially for septic shock patients with hypoxic respiratory failure. However, the 2021 Surviving Sepsis Campaign (SCC) guideline does not provide clear recommendations for mechanical ventilation. Reasons to initiate invasive mechanical ventilation include but are not limited to hypoxemia, acute respiratory failure either from primary lung injury or secondary acute respiratory distress syndrome (ARDS), reduced level of consciousness secondary to septic encephalopathy, and perceived risk of clinical worsening[6]. The decision to intubate is a complex, multifactorial process, and the optimal timing is currently unclear.

Some perspectives suggest that early initiation of invasive mechanical ventilation for patients with respiratory distress may help to avoid self-inflicted lung and diaphragm injuries, prevent the deterioration of respiratory failure, and promote recovery[7]. Some studies support this viewpoint[8,9]. However, the research by Mellado-Artigas and colleagues disagrees, suggesting that an early approach to invasive mechanical ventilation does not improve outcomes in patients with septic shock[10]. Another study suggests that intubation within 24 h of sepsis onset was not associated with hospital mortality but resulted in fewer 28-day hospital-free days. Tracheal intubation, as a high-risk procedure, did not increase the risk of mortality among septic shock patients with predominant hemodynamic compromise[11]. Therefore, the optimal timing of intubation is still controversial for patients with septic shock.

In this context, we conducted an observational cohort study using data from the Medical Information Mart in Intensive Care IV (MIMIC-IV) database. We aimed to assess the impact of intubation in septic shock patients within the first 8 h after vasopressor initiation (defined as early intubation), compared to non-early intubated controls, on 30-day and 90-day all-cause mortality.

Methods

Database

We extracted data using the Structured Query Language (SQL) from the MIMIC-IV database[12,13], which is an open-access public database that has collected clinical data from over 190,000 patients and 450,000 hospital admissions at Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019. Our first author, Jun Xu, obtained authorization to use this database (Authorization Number: 48615099). All patient information in the database has undergone de-identification and has been approved by the Institutional Review Board (IRB) at the Massachusetts Institute of Technology (MIT) and BIDMC. Therefore, the need for ethical approval and informed consent were waived for this research by the ethics committees of the first affiliated hospital, Zhejiang University School of Medicine. All methods and procedures were carried out in accordance with the Declaration of Helsinki.

Patients

We utilized the MIMIC-IV database, focusing on adult patients who developed septic shock and required the use of vasopressors within the first 24 h after their initial admission to the ICU. Patients were not eligible if vasopressors were initiated after endotracheal intubation and invasive mechanical ventilation.

The exclusion criteria of our study were as follows: (1) adult patients with multiple ICU admissions were only included in the analysis for their first ICU admission; (2) patients with suspected infection occurring more than 24 h before or after ICU admission; (3) patients who received vasopressors more than 24 h after ICU admission; (4) patients who received vasopressor infusion after endotracheal intubation.

The Sepsis-3 criteria for sepsis were extracted as suspected infection with associated organ dysfunction (Sequential Organ Failure Assessment (SOFA) ≥ 2). Patients with septic shock were identified with hypotension

requiring vasopressors to maintain a mean arterial pressure (MAP) of at least 65 mm Hg and a serum lactate level greater than 2 mmol/L according to the Sepsis-3 definition[14]. We defined the "early intubation group" as occurring in the first 8 h after vasopressor start based on previous research[10,15].

Outcomes

The primary outcomes were the 30 day and 90 day all-cause mortality rates after ICU admission. The secondary outcomes included the duration of mechanical ventilation and continuous renal replacement therapy (CRRT), urine output on the first and second day after ICU admission, and lengths of hospital and ICU stays.

Variables

We collected the potential confounders that may affect the mortality, including demographics, comorbid conditions (such as diabetes, congestive heart failure [CHF], myocardial infarction [MI], cerebrovascular disease, chronic obstructive pulmonary disease [COPD], mild liver disease, chronic kidney disease [CKD], malignancy, etc.), laboratory tests, disease severity, and treatment measures at the time of shock occurrence. The severity of the disease was represented by the Charlson comorbidity index (CCI), Simplified Acute Physiology Score (SAPS) II score, and SOFA score during the first 24 h of ICU admission. The patient's Glasgow Coma Scale (GCS) score at the time of intubation was also extracted. Treatments included fluid administration, antibiotics, corticosteroids, various vasopressors (such as norepinephrine, epinephrine, phenylephrine, dopamine, dobutamine, and vasopressin), CRRT, and the timing of these interventions.

Statistical methods

Continuous variables were reported as mean ± standard deviation or median (interquartile range [IQR]), depending on whether the data were normally distributed, and categorical variables were reported using numbers (%). For comparisons between the two groups, we used the Student's t-test or Kruskal–Wallis test for continuous variables and a chi-square test or Fisher's exact test for categorical variables as appropriate. A two-tailed P-value of 0.05 was considered significant for all analyses. All statistical analyses and plotting were conducted using Python (3.9) and R software (v4.2.3).

We performed multiple imputations using the mice package in R for missing data that accounted for less than 10%; otherwise, we excluded them.

Propensity score matching (PSM) analysis[16] is a method commonly used in observational studies aimed at reducing the bias caused by the differences in confounding variables between the intervention and control groups, thereby more accurately estimating the causal effect of the intervention. The PSM in our study used a 1:1 optimal matching method with a caliper of 0.02 of the standard deviation of the logit of the estimated propensity score. The logistic regression model used to construct the propensity score was: early intubation ~ age + sex + weight + comorbidities + disease severity + laboratory tests + interventions. We calculated the standardized mean difference (SMD) to assess the effectiveness of PSM in reducing differences between the early intubation group (first 8 h after vasopressor start) and the non-early intubation group (unexposed). We considered an SMD cutoff of 0.1 to represent a good adjustment.

Subsequently, all analyses were carried out in the matched population. We compared the early and non-early intubation groups' effects on primary and secondary outcomes in septic shock patients. For 30-day and 90-day all-cause mortality, Kaplan–Meier curves were derived, and the early intubated effect was estimated through a Cox proportional hazard model. We calculated the hazard ratio (HR) and 95% confidence interval (95% CI) and conducted pre-specified subgroup analyses of 30 day and 90 day mortality, reporting p-values for interaction. To test the robustness of our finding, we excluded patients who were not intubated and then analyzed the impact of early intubation compared to late intubation (beyond 8 h) on 30-day and 90-day all-cause mortality.

In addition, multivariate logistic regression was performed to determine the association between early intubation and 30 day and 90 day all-cause mortality rates. Age, sex, weight, CCI, SOFA score, lactate, blood culture positive, and treatments were used as covariates in multivariate analysis to adjust for patients. A variance inflation factor greater than 10 was used to indicate multicollinearity. Then, we used a restricted cubic spline multivariate logistic regression model to further analyze the non-linear association between endotracheal intubation timing and the risk of 30-day and 90-day all-cause mortality.

Results

Population

A total of 32,970 adult patients with sepsis were identified according to the Sepsis-3.0 definition. Based on our exclusion criteria, 6864 patients were selected and analyzed for the study. Of these, 2048 (29.8%) were intubated in the first 8 h at a median 0.3 h after vasopressor start (IQR 0.1–1 h). Among the remaining 4816 patients, 491 (10.2%) patients received intubation beyond 8 h (median 26.2, IQR 14.9–53.4 h), as depicted in Fig. 1.

As depicted in Table 1, there are notable differences in several baseline characteristics between the two groups in the original cohort, including age, sex, weight, comorbidities (CHF, MI, COPD, CKD, stroke, malignancy, and metastatic cancer), CCI, SAPS II score, SOFA score, platelet, PT, APTT, lactate, blood culture positivity, medication use, and CRRT.

After PSM, 2786 patients were successfully paired, consisting of 1393 individuals who received early intubation and 1393 who did not. Following matching, there was a good balance in baseline characteristics between the early intubation group and the non-early intubation group, with all variables having an SMD of less than 10% (see Additional file 1: Figure S1).

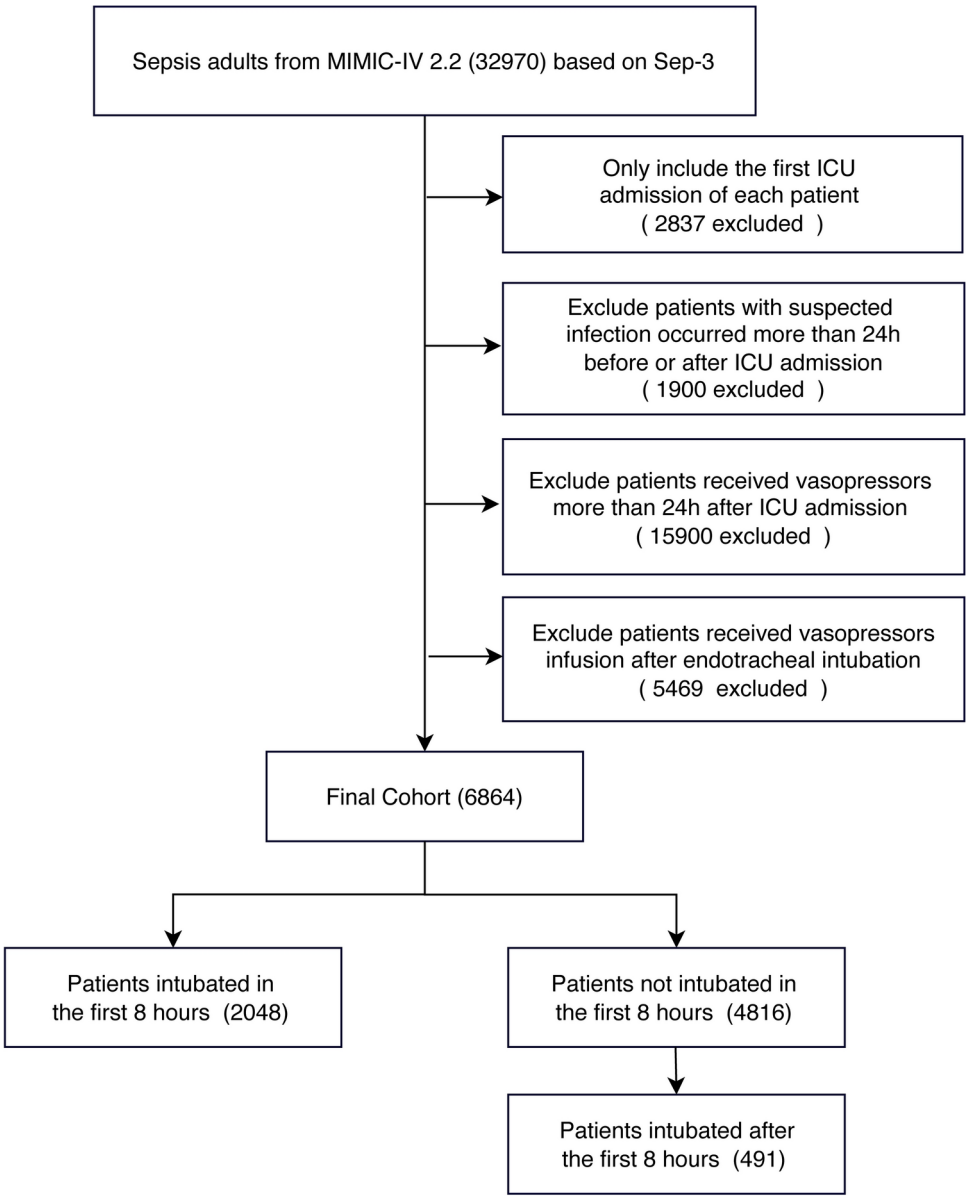

Fig.1. Study flowchart.

Association between early intubation and clinical outcomes

In the PSM cohort, the primary end point of death from any cause at 30 days occurred in 288 of 1393 patients (20.7%) in the early intubation group and in 381 of 1393 patients (27.4%) in the non-early intubation group (Table 2). In time-to-event analyses, a significant difference was observed between the treatment groups (HR 0.717; 95% CI 0.616–0.836; $p < 0.001$ by the log-rank test) (Fig. 2A); Similarly, at 90 days, death had occurred in 366 (26.3%) in the early intubation group, as compared with 453 (32.5%) in the non-early intubation. The result indicated that early intubation was associated with a lower 90-day mortality rate (HR 0.761; 95% CI 0.663–0.874; $p < 0.001$) (Additional file 1: Figure S2A).

Several differences in secondary outcomes were observed in our study. First, the urine volume in the early intubation group was significantly higher on day 1 (1.8 vs. 1.7 L; $p = 0.003$) and day 2 (1.7 vs. 1.4 L; $p < 0.001$). Second, although early intubation was associated with a reduction in mortality, we found that it prolonged hospital stay (8.9[5.4,15.1] vs. 7.2[4.5,12.0]; $p < 0.001$) and extended ICU stay (3.6 [1.9,7.1] vs. 2.3 [1.3,4.3]; $p < 0.001$). Additionally, it is intriguing to note that, compared to the unexposed group, the early intubation group had a shorter mechanical ventilation duration (3.2 vs. 4.3; $p = 0.017$). However, the two groups had no significant difference in the duration of CRRT use (Table 2).

Subgroup analysis and sensitivity analysis

As shown in Fig. 2B, within subgroups stratified by factors such as age, sex, SOFA score, blood culture positivity, and glucocorticoid use, no significant interactions were observed (P-interaction > 0.05). This suggests that the

Early intubation	Before matching				After matching			
	YES	NO	P value	SMD	YES	NO	P value	SMD
Number of subjects	2048	4816			1393	1393		
Age	66.8 ± 14.9	68.9 ± 14.1	< 0.001	0.138	67.6 ± 14.4	67.5 ± 14.4	0.842	0.008
Sex, male (%)	791 (38.6)	2025 (42.0)	0.009	0.070	552 (39.6)	554 (39.8)	0.969	0.003
Weight(kg)	85.1 ± 25.8	81.4 ± 24.6	< 0.001	0.145	83.9 ± 25.4	84.2 ± 31.0	0.772	0.011
Comorbidities (%)								
Diabetes	657 (32.1)	1572 (32.6)	0.670	0.012	436 (31.3)	444 (31.9)	0.775	0.012
CHF	763 (37.3)	1637 (34.0)	0.010	0.068	500 (35.9)	513 (36.8)	0.636	0.019
MI	484 (23.6)	957 (19.9)	0.001	0.091	308 (22.1)	322 (23.1)	0.556	0.024
COPD	612 (29.9)	1211 (25.1)	< 0.001	0.106	391 (28.1)	385 (27.6)	0.833	0.010
Liver	318 (15.5)	718 (14.9)	0.536	0.017	212 (15.2)	211 (15.1)	1.000	0.002
Renal	484 (23.6)	1261 (26.2)	0.029	0.059	320 (23.0)	319 (22.9)	1.000	0.002
Stroke	257 (12.5)	402 (8.3)	< 0.001	0.138	151 (10.8)	149 (10.7)	0.951	0.005
Rheumatic disease	70 (3.4)	204 (4.2)	0.129	0.043	51 (3.7)	47 (3.4)	0.758	0.016
Malignancy	223 (10.9)	750 (15.6)	< 0.001	0.139	168 (12.1)	172 (12.3)	0.862	0.009
Metastatic cancer	99 (4.8)	347 (7.2)	< 0.001	0.100	69 (5.0)	80 (5.7)	0.400	0.035
AIDS	13 (0.6)	54 (1.1)	0.082	0.052	10 (0.7)	4 (0.3)	0.180	0.061
Severity of the disease								
GCS	13.7 ± 3.2	13.7 ± 2.6	0.923	0.002	13.7 ± 3.2	13.7 ± 2.8	0.748	0.012
CCI	5.2 ± 2.8	5.5 ± 2.9	0.001	0.089	5.2 ± 2.7	5.3 ± 2.9	0.546	0.023
SAPS II score	48.5 ± 15.7	39.0 ± 13.7	< 0.001	0.645	44.5 ± 13.5	44.4 ± 16.1	0.823	0.008
SOFA score	4.4 ± 2.2	4.0 ± 1.9	< 0.001	0.207	4.2 ± 2.1	4.1 ± 2.0	0.565	0.022
Respiratory	0.7 ± 1.0	0.4 ± 0.7	< 0.001	0.324	0.6 ± 0.9	0.6 ± 0.9	0.706	0.014

Table 1. Baseline characteristics between groups before and after PSM.

Early intubation	Before matching			After matching		
	YES	NO	P-Value	YES	NO	P-Value
Number of subjects	2048	4816		1393	1393	
Primary outcome						
30-day mortality (%)	531 (25.9)	900 (18.7)	< 0.001	288 (20.7)	381 (27.4)	< 0.001
90-day mortality (%)	650 (31.7)	1252 (26.0)	< 0.001	366 (26.3)	453 (32.5)	< 0.001
Secondary outcomes						
Urine day 1 (L)	1.7 ± 1.6	1.9 ± 1.3	< 0.001	1.8 ± 1.3	1.7 ± 1.3	0.003
Urine day 2 (L)	1.6 ± 1.4	1.5 ± 1.2	< 0.001	1.7 ± 1.4	1.4 ± 1.3	< 0.001
Length of MV, days	3.6 ± 6.6	4.0 ± 5.5	0.247	3.2 ± 6.4	4.3 ± 6.5	0.017
Length of CRRT, days	7.2 ± 24.8	3.9 ± 4.3	0.074	9.1 ± 35.3	3.9 ± 4.5	0.153
ICU LOS, days, median (IQR)	3.8 (1.9,7.9)	2.2 (1.4,3.8)	< 0.001	3.6 (1.9,7.1)	2.3 (1.3,4.3)	< 0.001
Hospital LOS, days, median (IQR)	9.0 (5.3,15.8)	7.0 (4.7,11.7)	< 0.001	8.9 (5.4,15.1)	7.2 (4.5,12.0)	< 0.001

Table 2. Primary and secondary outcomes analysis between groups before and after PSM. *ICU* intensive care unit, *IQR* interquartile range, *MV* mechanical ventilation *CRRT* continuous renal replacement therapy, *LOS* length of stay.

results derived from the matched population are reliable, indicating a significant association between early intubation and a reduced 30 day mortality rate. However, in the subgroup analysis regarding the 90 day mortality rate (Additional file 1: Figure S2B), the association between early intubation and 90 day mortality was different in the population under 65 years old and over 65 years old (P-interaction = 0.007).

To further verify our results, we excluded patients who were not intubated and retained data from 2539 intubated patients: 2048 were intubated early (in the first 8 h), and 491 were intubated late (beyond 8 h). Using the same 1:1 PSM method, 422 pairs with good adjustment were identified (Additional file 1: Table S1). In survival analysis, we still observed the same results in the PSM cohort, where early intubation was associated with a lower 30 day mortality rate (HR 0.661; 95% CI 0.527–0.828; $p < 0.001$) and a 90 day mortality rate (HR 0.680; 95% CI 0.552–0.838; $p < 0.001$) (Fig. 3A; Additional file 1: Figure S3A).

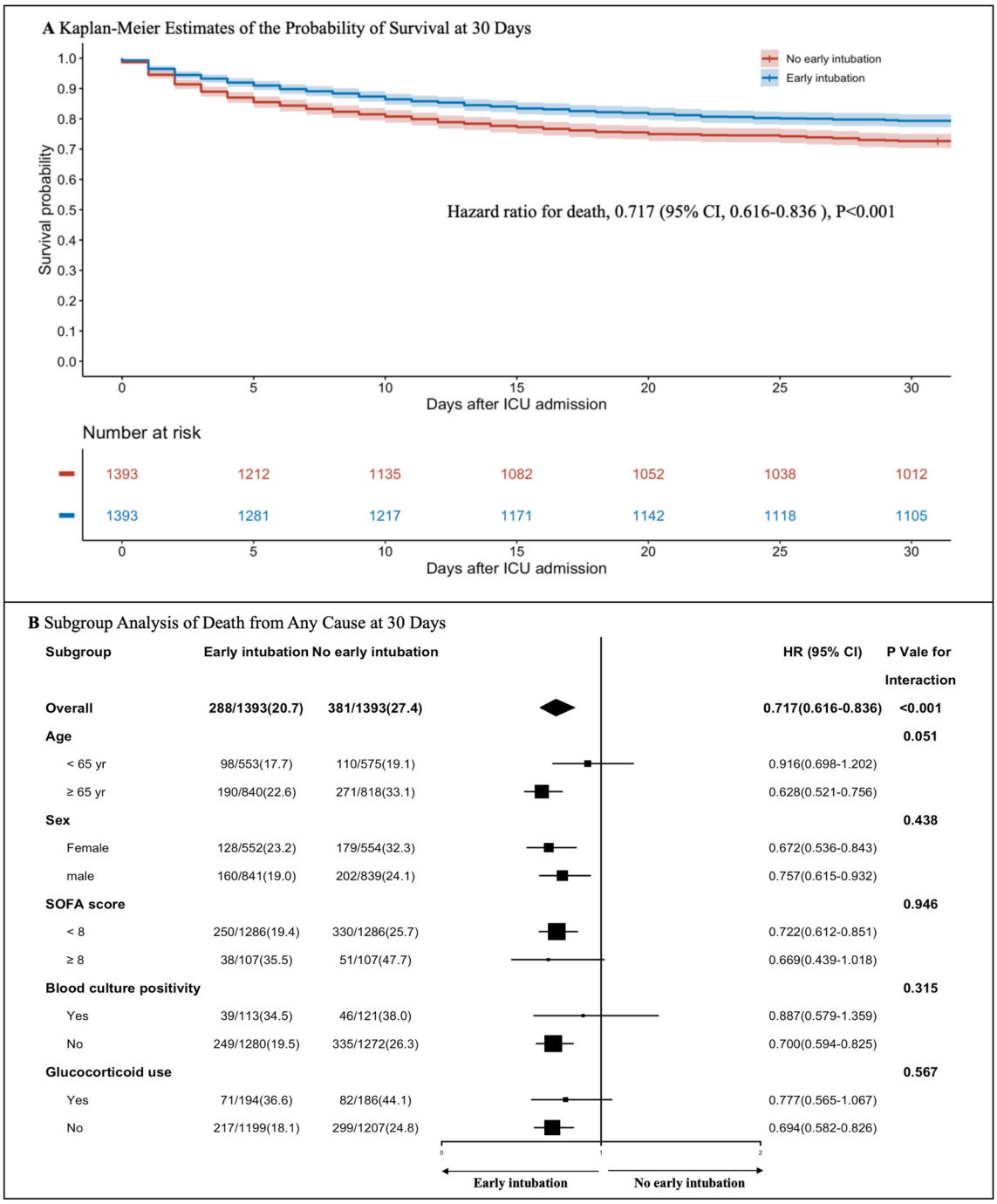

Fig.2. Probability of survival and hazard ratio for death at 30 days. Panel A shows Kaplan–Meier estimates of the probability of survival at 30 days, which was a significant difference among the patients in the early intubation group and among those in the non-early intubation group (hazard ratio for death from any cause, 0.717; 95% CI, 0.616 to 0.836). Panel B shows the hazard ratio with 95% confidence intervals for death from any cause within 30 days after grouping in five prespecified subgroups.

Additionally, we found that in the predefined subgroup analyses, there was no significant heterogeneity in the early intubation effect on mortality at 30 or 90 days, except for the age group (Fig. 3B; Additional file 1: Figure S3B).

Restricted cubic spline model

Multivariate logistic regression was used to analyze factors that might affect 30-day or 90-day mortality. Factors that might influence mortality were included in the analysis, including early intubation, age, sex, weight, CCI,

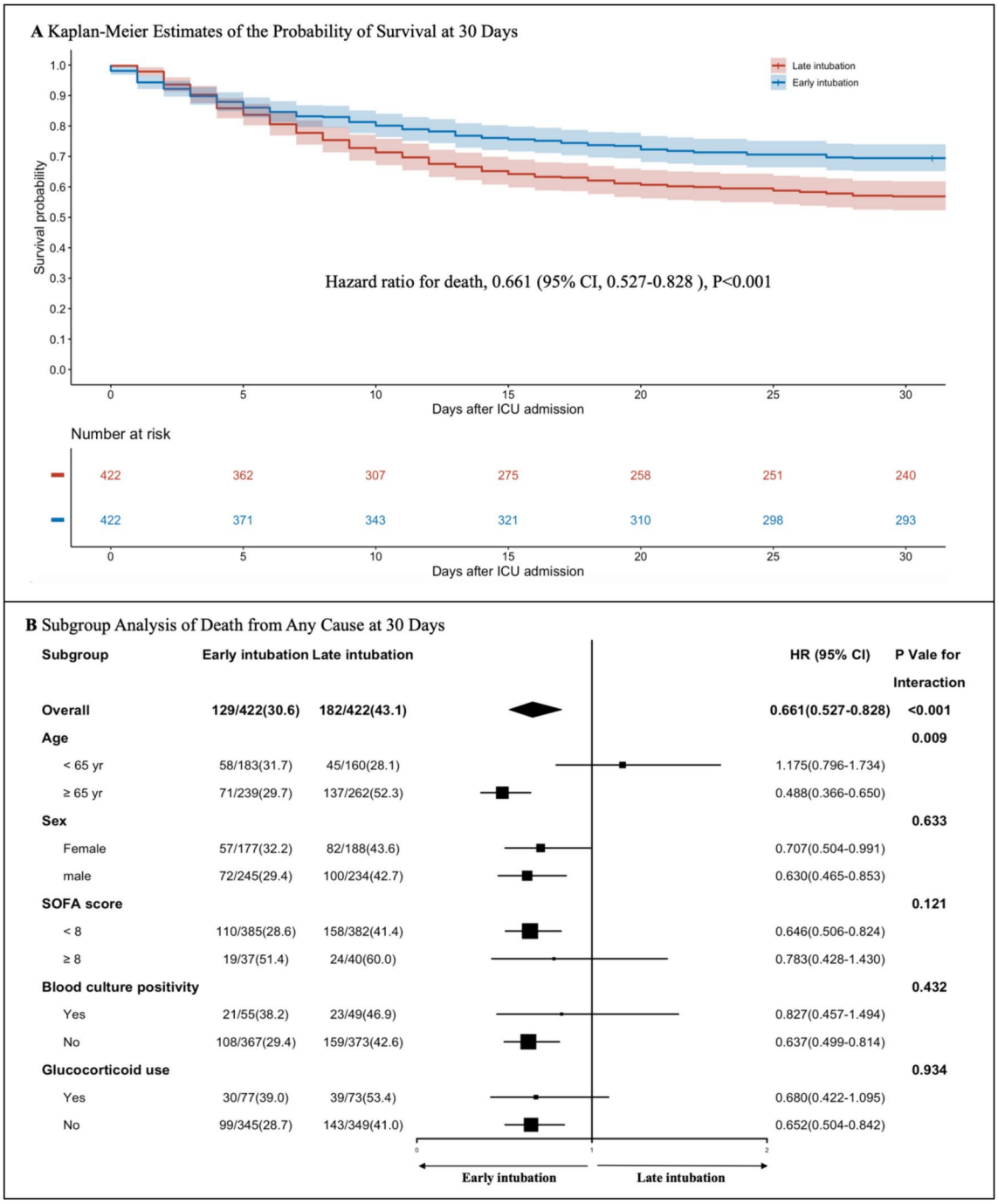

Fig.3. Comparison between patients who were intubated early or late (beyond 8 h) after PSM. Panel A shows Kaplan–Meier estimates of the probability of survival at 30 days, which was a significant difference among the patients in the early intubation group and among those in the late intubation group (hazard ratio for death from any cause, 0.661; 95% CI, 0.527 to 0.828). Panel B shows the forest plot of the risk of death from any cause at 30 days among patients intubated early or late in five prespecified subgroups.

SOFA score, lactate, blood culture positivity, medication use, and CRRT (Table 3). Similar results showed that early intubation was still an independent protective factor for 30-day or 90-day mortality.

In addition, we used a restricted cubic spline (RCS) model to further investigate the association between intubation timing and 30-day all-cause mortality. In this model, the association between intubation timing and 30-day all-cause mortality was an inverse U-shaped, as shown in Fig. 4 (P-overall = 0.001), adjusted for variables including age, weight, CCI, SOFA score, lactate, and medication use (antibiotic, glucocorticoid, norepinephrine, epinephrine, dopamine, and vasopressin). If we used an RCS to study the relationship between intubation timing

Variables	30 day		90 day	
	OR (95%CI)	P-Value	OR (95%CI)	P-Value
Early intubation	0.603(0.49–0.741)	< 0.001	0.659(0.541–0.8)	< 0.001
Age	1.014(1.005–1.023)	0.002	1.01(1.002–1.019)	0.017
Sex	1.163(0.937–1.444)	0.171	1.129(0.919–1.386)	0.249
Weight	0.993(0.988–0.998)	0.005	0.993(0.989–0.998)	0.003
CCI	1.204(1.153–1.258)	< 0.001	1.274(1.22–1.33)	< 0.001
SOFA score	1.027(0.976–1.08)	0.305	1.017(0.968–1.068)	0.499
Lactate	1.13(1.092–1.17)	< 0.001	1.11(1.073–1.15)	< 0.001
Blood culture positivity	1.02(0.732–1.413)	0.905	1.277(0.928–1.754)	0.131
Antibiotic use	0.72(0.581–0.892)	0.003	0.799(0.652–0.978)	0.030
Glucocorticoid use	1.468(1.118–1.923)	0.006	1.502(1.152–1.955)	0.003
Norepinephrine	3.709(2.726–5.076)	< 0.001	3.69(2.777–4.924)	< 0.001
Epinephrine	0.689(0.493–0.955)	0.027	0.668(0.484–0.916)	0.013
Phenylephrine	1.233(0.971–1.565)	0.085	1.195(0.948–1.509)	0.132
Dopamine	1.884(1.352–2.621)	< 0.001	2.034(1.468–2.822)	< 0.001
Dobutamine	1.561(0.953–2.559)	0.077	1.464(0.89–2.424)	0.135
Vasopressin	2.716(2.111–3.499)	< 0.001	2.451(1.907–3.154)	< 0.001
CRRT	1.247(0.763–2.036)	0.377	1.327(0.812–2.183)	0.261

Table 3. Multivariate logistic regression analysis of risk factors for 30 day and 90 day mortality in patients with septic shock after PSM. *CCI* Charlson comorbidity index, *SOFA* sequential organ failure assessment, *CRRT* continuous renal replacement therapy, *OR* odds ratio, *CI* confidence interval.

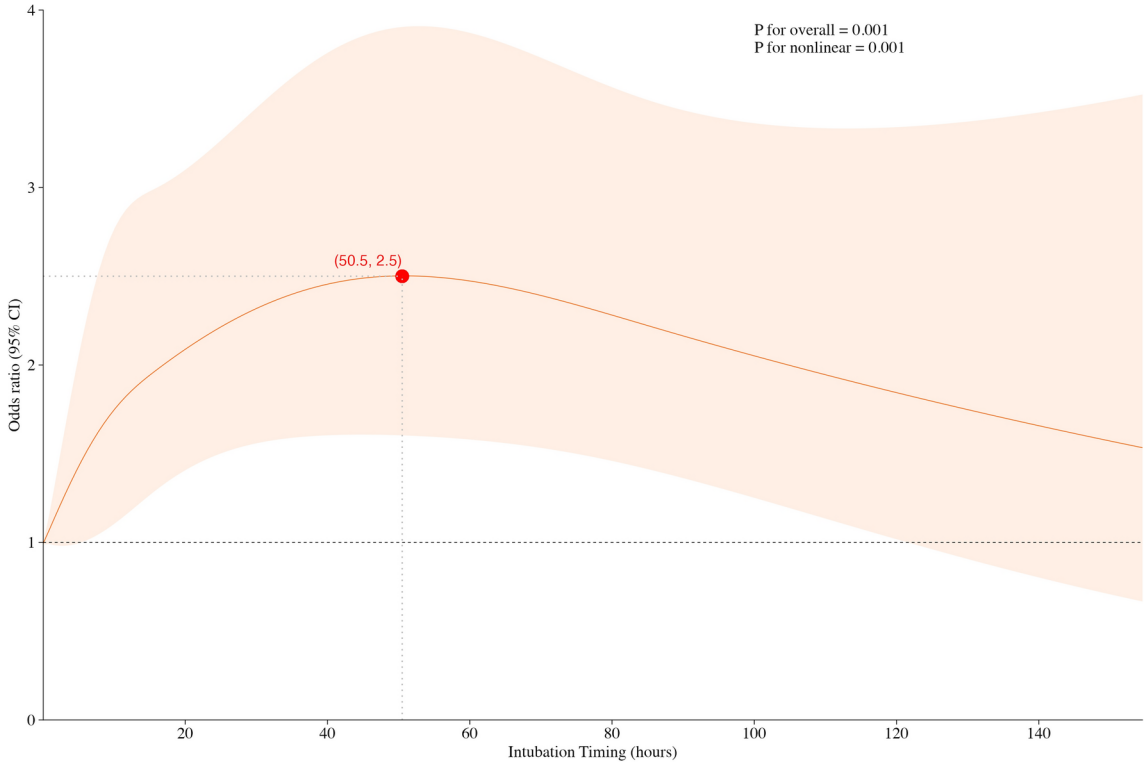

Fig.4. Association with intubation timing and 30-day all-cause mortality, adjusted variables including age, weight, CCI, SOFA score, lactate, and medication use (antibiotic, glucocorticoid, norepinephrine, epinephrine, dopamine, and vasopressin).

and 90 day mortality, it was not difficult to find that as the time of intubation extended, the risk of death at 90 days gradually increased (Additional file 1: Figure S4).

Discussion

In this retrospective cohort study, we aimed to investigate the effect of early intubation on the mortality rates of septic shock patients within 30 and 90 days, comparing it with a non-early intubation approach during the same periods. Our research findings indicated a significant association between early intubation (within the first 8 h following the initiation of vasopressor) in septic shock patients in the ICU and lower 30 day and 90 day all-cause mortality rates. Meanwhile, the association between intubation timing and all-cause 30 day mortality was an inverse U-shaped relationship, reaching the highest risk around 50.5 h and then decreasing thereafter. Conversely, our study found that early intubation actually prolonged hospital and extended ICU stays.

In our subgroup analysis, we further confirmed the robustness of the results obtained from the overall population. Additionally, we found that statistically significant differences in early intubation and 30-day mortality remained in certain subpopulations. These subpopulations were stratified by factors such as age, sex, SOFA score, blood culture positivity, and glucocorticoid use. However, the benefit of early intubation in reducing 90-day mortality was not seen in those younger than 65 years old. Sensitivity analysis showed that in the subgroup of individuals aged 65 or older, early intubation can reduce mortality rates at 30 and 90 days; on the contrary, early intubation was associated with an increased mortality rate in individuals younger than 65.

Previous studies have suggested that delayed tracheal intubation may increase mortality[9,17,18]. A meta-analysis[8], which included data on 15,441 critically ill patients without COVID-19 across 27 studies, also demonstrated that all-cause mortality was lower in patients undergoing early versus late intubation. However, these studies often pertain to critically ill patients with acute respiratory failure caused by pneumonia rather than those with septic shock. Of course, some patients with pneumonia may also have septic shock. The study concerning COVID-19 patients reached a similar conclusion, indicating that early tracheal intubation may be an independent protective factor for mortality[19]. However, Mellado-Artigas et al. reached a different conclusion for patients with septic shock[10]. They reported that early intubation did not improve in-hospital mortality or ICU and hospital lengths of stay in patients with septic shock compared to non-early intubation. When patients intubated late were compared to those intubated early, mortality was also unchanged between groups in their study. Therefore, they suggested that while delayed intubation may be harmful by itself, avoiding intubation in many patients may offset the benefits of early intubation. The condition may be more pronounced in patients with less severe disease. Their findings were in line with an analysis involving individuals with GCS scores ≤ 8 after major trauma[20] and a meta-analysis of observational studies in COVID-19[21].

However, our findings did not align with the results of Mellado-Artigas et al. In our study, we compared the effects of early and non-early (or late) intubation in patients with septic shock. We found that early intubation was strongly associated with lower 30-day and 90-day mortality rates, regardless of the disease severity. For patients aged 65 and above, the effect may be stronger. We also found that early intubation was an independent protective factor in the multivariate logistic regression model. The RCS curve further showed that the risk of death increases with delays in tracheal intubation within 0–50.5 h. In a correspondence by Jianmin Qu et al.[22], concerns were raised about the study design and statistics used by Mellado-Artigas et al. They suggested that while most variables were balanced in the matched cohort, there may still be hidden biases due to unmeasured confounding factors. Regrettably, this could also be an issue in our own study.

The 2021 SSC guidelines suggest that there is insufficient evidence to recommend the use of invasive ventilation in comparison to non-invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure[5]. So, ICU physicians must weigh the potential advantages and disadvantages of using invasive mechanical ventilation versus non-invasive oxygenation strategies and then decide when to perform intubation. The balance of benefit and harm from intubation may change as patients progress through the acute phase of illness. The timing of intubation for invasive ventilation is often described as "early intubation vs. delayed intubation", but this terminology may not be ideal. According to Christopher J. Yarnell et al.[23], it might be more appropriate to rephrase the question of when to intubate as "what physiological threshold can identify patients who would benefit from invasive ventilation". Choosing a lower physiological threshold for severity for invasive ventilation will result in more procedures being performed, offering the benefit of avoiding severe complications such as preventing exacerbations, emergency intubation, and self-inflicted lung injury. This also involves significant resource consumption and risk of injury, including intubation-induced shock and cardiac arrest, laryngeal trauma, VAP, delirium, and ICU-acquired muscle weakness.

A single physiological threshold that indicates the need for intubation can be the arterial oxygen partial pressure ratio to fractional inspired oxygen (PaO2/FiO2). For instance, a large cohort study conducted on patients with ARDS showed that for patients with a PaO2/FiO2 ratio less than 150 mm Hg, the mortality rate with invasive ventilation was lower than that with non-invasive ventilation[24]. A prospective multicenter observational study[15] showed that seven influencing factors were significantly associated with early intubation, in descending order of significance: GCS score, central effect, use of auxiliary respiratory muscle, lactate level, vasoconstrictor dose, pH, and airway self-cleaning ability. In their study, neurological, respiratory, and hemodynamic parameters only partially explained the use of tracheal intubation in septic shock patients. Scoring scales similar to those that guide the decision to start a VV-ECMO, such as the Murray Score (Lung Injury Score) and RESP score[25], are also good options. In addition, artificial intelligence (AI) and machine learning have entered the field of medicine[26]. Machine learning can predict the need for intubation in critically ill patients using commonly collected bedside clinical parameters and laboratory results[27]. It may be used in real-time to help clinicians predict the need for intubation within 24 h of ICU admission, thereby avoiding delayed intubation.

This study has several limitations. First, this was a retrospective study based on MIMIC-IV database, which may be subject to information bias. The database itself may contain coding errors, outliers, and missing values,

even though we performed multiple imputations for a small amount of missing data. Second, sample selection may be influenced or unknown factors, resulting in samples that are not representative in certain aspects. Third, to balance the baseline characteristics between the two groups, we employed the PSM method to match a large number of confounding factors, but the hidden biases remain a possibility. Fourth, we artificially considered an 8-h window as a time frame to define early intubation based on previous research. Finally, we did not categorize the possible sources of septic shock.

Conclusions

In this matched cohort of septic shock patients, intubation within the first 8 h after the initiation of vasopressors conferred significant benefits in terms of both early and late mortality rates. After this time point, approximately 10% of patients underwent late intubation, which was associated with a more pronounced increase in mortality. Furthermore, this study further demonstrated that the timing of intubation showed an inverse U-shaped association with the 30 day all-cause mortality rate, with the peak risk of death occurring at 50.5 h after septic shock.

Data availability

Publicly available datasets were analyzed in this study. This data can be found here: Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R. MIMIC-IV (version 2.2). PhysioNet (https://doi.org/https://doi.org/10.13026/6mm1-ek67).

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References

1. Wong, I. M. J., Ferguson, N. D. & Urner, M. Invasive mechanical ventilation. *Intensive Care Med.* **49**, 669–672 (2024).
2. Telias, I. et al. The physiological underpinnings of life-saving respiratory support. *Intensive Care Med.* **48**, 1274–1286 (2022).
3. Slutsky, A. S. & Ranieri, V. M. Ventilator-induced lung injury. *N. Engl. J. Med.* **370**, 980 (2014).
4. Kalil, A. C. et al. Management of adults with hospital-acquired and ventilator-associated Pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin. Infect. Dis.* **63**, e61-111 (2016).
5. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med [Internet]. 2021 [cited 2021 Oct 2]; Available from: https://link.springer.com/https://doi.org/10.1007/s00134-021-06506-y
6. Maccagnan Pinheiro Besen, B. A., Tomazini, B. M. & Pontes Azevedo, L. C. Mechanical ventilation in septic shock. *Curr. Opin. Anaesthesiol.* **34**, 107–112 (2021).
7. Lee KG, Roca O, Casey JD, Semler MW, Roman-Sarita G, Yarnell CJ, et al. When to intubate in acute hypoxaemic respiratory failure? Options and opportunities for evidence-informed decision making in the intensive care unit. The Lancet Respiratory Medicine [Internet]. 2024 [cited 2024 Jun 4];S2213260024001188. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260024001188
8. Xixi, & N, A. Association between timing of intubation and clinical outcomes of critically ill patients: A meta-analysis. *J. Crit. Care* **71**, 154062 (2022).
9. Kangelaris, K. N. et al. Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome. *Crit. Care Med.* **44**, 120–129 (2016).
10. Mellado-Artigas, R. et al. Early intubation and patient-centered outcomes in septic shock: a secondary analysis of a prospective multicenter study. *Crit. Care.* **26**, 163 (2022).
11. Yang, T. et al. Outcome after intubation for septic shock with respiratory distress and hemodynamic compromise: an observational study. *BMC Anesthesiol.* **21**, 253 (2021).
12. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R. MIMIC-IV (version 2.2). PhysioNet [Internet]. 2023; Available from: https://doi.org/10.13026/6mm1-ek67
13. Johnson, A. E. W. et al. MIMIC-IV, a freely accessible electronic health record dataset. *Sci. Data* **10**, 1 (2023).
14. Singer, M. et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* **315**, 801 (2022).
15. Darreau, C. et al. Use, timing and factors associated with tracheal intubation in septic shock: a prospective multicentric observational study. *Ann. Intensive Care.* **10**, 62 (2024).
16. Deb, S. et al. A Review of propensity-score methods and their use in cardiovascular research. *Can. J. Cardiol.* **32**, 259–265 (2016).
17. Dumas, G. et al. Survival in immunocompromised patients ultimately requiring invasive mechanical ventilation: a pooled individual patient data analysis. *Am. J. Respir. Crit. Care Med.* **204**, 187–196 (2021).
18. Kang, B. J. et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med.* **41**, 623–632 (2015).
19. Manrique, S. et al. Timing of intubation and ICU mortality in COVID-19 patients: a retrospective analysis of 4198 critically ill patients during the first and second waves. *BMC Anesthesiol.* **23**, 140 (2023).
20. Soni, K. D. et al. Intubation and in-hospital mortality after trauma with glasgow coma scale score eight or less—a cohort study. *J. Surg. Res.* **299**, 188–194 (2024).
21. Papoutsi, E. et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Crit. Care.* **25**, 121 (2021).
22. Qu, J., Shen, Y. & Zhang, H. Early intubation and patient-centered outcomes in septic shock. *Crit. Care* **26**, 299 (2022).
23. Yarnell, C. J. & Patel, B. K. When should we intubate in hypoxemic respiratory failure. *NEJM Evid.* **2**, 2200305 (2023).
24. Bellani, G. et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. insights from the LUNG SAFE study. *Am. J. Respir. Crit. Care Med.* **195**, 67–77 (2017).
25. Tonna, J. E. et al. Management of adult patients supported with venovenous extracorporeal membrane oxygenation (VV ECMO): guideline from the extracorporeal life support organization (ELSO). *ASAIO J.* **67**, 601–610 (2021).
26. Haug, C. J. & Drazen, J. M. Artificial intelligence and machine learning in clinical medicine, 2023. *N. Engl. J. Med.* **388**, 1201–1208 (2023).
27. Siu, B. M. K., Kwak, G. H., Ling, L. & Hui, P. Predicting the need for intubation in the first 24 h after critical care admission using machine learning approaches. *Sci. Rep.* **10**, 20931 (2020).

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Author contributions

Jun Xu: extracted the data, analyzed the data, and drafted the manuscript; Jian Chen: contributed to the grammar check; Hongliu Cai: contributed to the preparation of figures and tables; Xia Zheng: supervised the project and provided critical revisions to the manuscript. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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