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The Association Between Time From Emergency Department Visit to ICU Admission and Mortality in Patients With Sepsis

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OBJECTIVES: The Surviving Sepsis Campaign Guidelines 2021 recommends that adult patients with sepsis requiring intensive care should be admitted to the ICU within 6 hours of their emergency department (ED) visits. However, there is limited evidence on whether 6 hours is the best target time for compliance with the sepsis bundle. We aimed to investigate the association between time from ED visits to ICU admission (i.e., ED length of stay [ED-LOS]) and mortality and identify the optimal ED-LOS for patients with sepsis.

DESIGN: Retrospective cohort study.

SETTING: The Medical Information Mart for Intensive Care Emergency Department and Medical Information Mart for Intensive Care IV databases.

PATIENTS: Adult patients (≥ 18 yr old) who were transferred from the ED to the ICU and subsequently diagnosed with sepsis based on the Sepsis-3 criteria within 24 hours of ICU admission.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among 1,849 patients with sepsis, we found a disproportionally higher mortality rate in patients immediately admitted to the ICU (e.g., < 2 hr). When using ED-LOS as a continuous variable, ED-LOS was not significantly associated with 28-day mortality (adjusted odds ratio [OR] per hour increase, 1.04; 95% CI, 0.96–1.13; $p = 0.3$) after an adjustment for potential confounders (e.g., demographics, triage vital signs, and laboratory results) in the multivariable analysis. However, when we categorized all patients into time quartiles (ED-LOS: < 3.3 hr, 3.3–4.5 hr, 4.6–6.1 hr, and > 6.1 hr), patients in the higher time quartiles (e.g., 3.3–4.5 hr) had higher 28-day mortality compared with those in the lowest time quartile (< 3.3 hr) (e.g., adjusted OR for patients in the second time quartile [3.3–4.5 hr] 1.59; 95% CI, 1.03–2.46; $p = 0.04$).

CONCLUSIONS: Earlier admission to the ICU (e.g., within 3.3 hr of ED visits) was associated with lower 28-day mortality in patients with sepsis. Our findings suggest patients with sepsis who require intensive care may benefit from a more immediate ICU admission than 6 hours.

KEY WORDS: emergency department length of stay; emergency department boarding; intensive care unit; sepsis; surviving sepsis campaign; sepsis bundle

Sepsis is a leading cause of death and critical illness worldwide (1, 2), and rapid assessment and appropriate intervention based on sepsis bundles are necessary to decrease the mortality of sepsis (3, 4). Delayed admission of patients with suspected sepsis from the emergency department (ED) to the ICU is associated with lower compliance with the sepsis bundle, higher mortality, longer duration of ventilator use, and longer ICU and hospital stay (5). Therefore, the Surviving Sepsis Campaign Guidelines (SSCG) 2021 suggested that patients with

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KEY POINTS

Question: What is the best target time from the emergency department (ED) visit to the ICU admission (i.e., ED length of stay [LOS]) for patients with sepsis requiring intensive care?

Findings: Patients with sepsis in the higher ED-LOS quartiles (i.e., > 3.3 hr) had higher 28-day mortality compared with those in the lower ED-LOS quartile (i.e., < 3.3 hr).

Meanings: Patients with sepsis who require intensive care may benefit from a more immediate ICU admission (e.g., 3 hr) than 6 hours based on the suggestion by the Surviving Sepsis Campaign Guidelines 2021.

sepsis who require intensive care should be admitted to the ICU within 6 hours of their ED visits (3, 4).

The suggestion by the SSCG 2021 is grounded on a previous study that estimated a 1.5% mortality increase for every hour delay in ICU admission for critically-ill patients (6), and several studies have proposed specific time targets from the ED visit to the ICU admission (i.e., ED length of stay [ED-LOS]) of 2.4, 3, and 6 hours (7–9). However, as these findings are based on studies analyzing the data on heterogeneous critically-ill patients with and without sepsis, there are no studies on the optimal ED-LOS in patients with sepsis to directly support the recommendations by the SSCG 2021. Furthermore, there are conflicting findings as to whether ICU admissions within 6 hours of ED visits are associated with better prognostic outcomes among patients with sepsis (10, 11). Thus, there is a dearth of evidence that quantifies within how many hours patients with sepsis should be admitted to the ICU.

To address these knowledge gaps, we aimed to investigate the association between ED-LOS and mortality and identify the optimal ED-LOS for patients with sepsis who require intensive care based on the sepsis bundles.

MATERIALS AND METHODS

Study Design and Setting

This is a retrospective cohort study using the data from the Medical Information Mart for Intensive Care Emergency Department (MIMIC-IV-ED) dataset version 1.0 (12) and the Medical Information Mart for Intensive Care (MIMIC-IV) dataset version 1.0 (13). MIMIC-IV is an extensive, publicly available database consisting of de-identified health-related data from over 60,000 patients admitted to the ICUs of the Beth Israel Deaconess Medical Center in the United States from 2008 to 2019 (13). MIMIC-IV-ED is a large publicly available dataset of over 40,000 patients who visited the ED of the Beth Israel Deaconess Medical Center from 2011 to 2019 (12). Approval by the research ethics committee was not needed for this study because MIMIC-IV and MIMIC-IV-ED databases are de-identified according to the HIPAA (HIPAA) Safe Harbor provision, and only credentialed authors who signed and conformed to the specified data use agreement accessed and analyzed the data (12, 13). Because of this, the TXP Medical Ethical Review Board waived the requirement for the ethical approval statement and informed consent (TXPREC-008).

Study Participants

The inclusion and exclusion criteria are shown in **Figure 1**. We identified adult patients (aged ≥ 18 yr) who were admitted to the ICU directly within 9 hours of the ED visit and met the diagnostic criteria for sepsis based on the Sepsis-3 criteria (14) within 24 hours of ICU admission from MIMIC-IV and MIMIC-IV-ED databases. Our analysis was limited to patients initially triaged at the resuscitated or emergency level, which requires compliance with the sepsis bundle (3, 4). We excluded patients who were transported from other hospitals, those who had a cardiac arrest or trauma at the ED arrival, those who died at the ED, and those who had missing data on all vital signs (i.e., systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], and body temperature [BT]) at the ED triage or all initial laboratory variables (i.e., sodium, potassium, lactate, blood urea nitrogen [BUN], creatinine, WBC, hemoglobin, and platelet count) on ICU admission.

Measurements

For each patient, we collected the following covariates: patient demographics (age, sex, and race/ethnicity [non-Hispanic White, non-Hispanic Black, Hispanic,

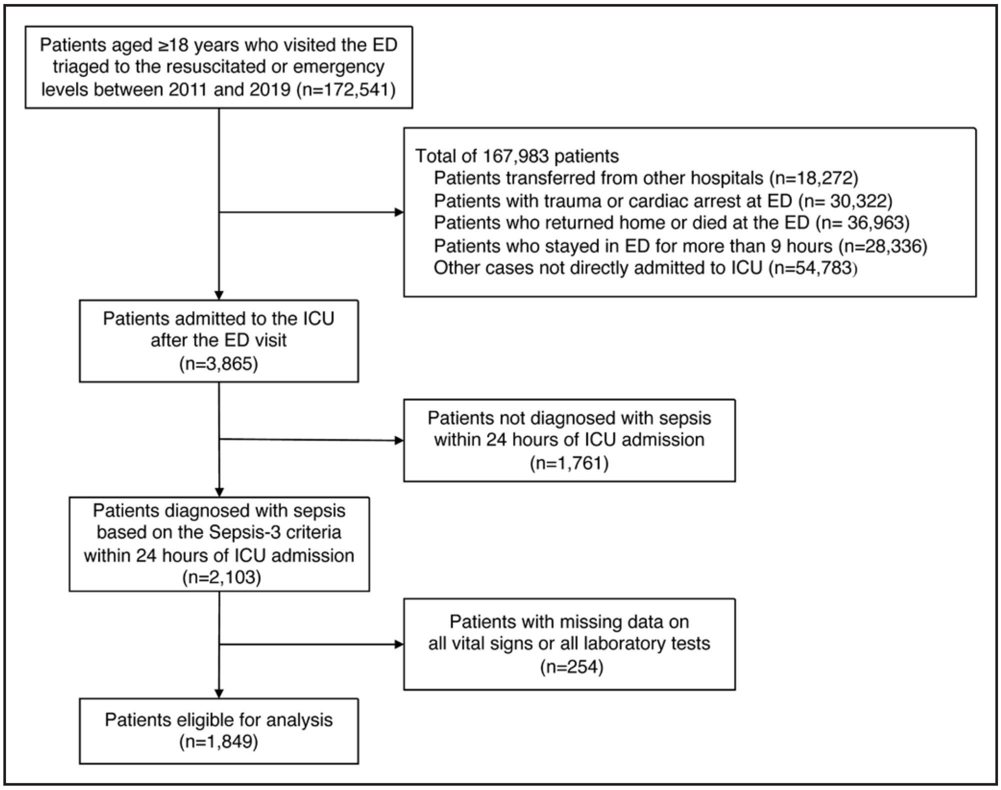

Figure 1. Flowchart of patient selection. ED = emergency department.

and others]), initial vital signs (SBP, DBP, HR, RR, and BT) and the counts of Systemic Inflammatory Response Syndrome [SIRS] qualifying categories at ED arrival, initial laboratory data on ICU admission (sodium, potassium, lactate, BUN, creatinine, WBC, hemoglobin, and platelet count), the maximum Sequential Organ Failure Assessment [SOFA] score within 24 hours of ICU admission. The exposure was time from the ED visit to ICU admission (i.e., ED length of stay [ED-LOS]) and the primary outcome was 28-day mortality. We considered patients who were discharged or were transferred from the ICU within 28 days as those who survived for 28 days after ICU admission.

Statistical Analyses

First, we treated outliers as missing and imputed all missing values using the MissForest algorithm, a nonparametric machine learning-based imputation method (15). The valid ranges of variables defining outliers and the percentage of missing values are shown in **Supplemental Table 1**, http://links.lww.com/CCX/B191.

We used summary statistics to delineate the patient characteristics of all patients and each patient in the ED-LOS quartiles. Continuous variables were expressed as medians and interquartile ranges (IQRs). Categorical variables were summarized as counts (*n*) and percentages (%).

Second, we visualized the association between ED-LOS and 28-day mortality using a locally weighted scatterplot smoother (Lowess) curve given that the relationship between the exposure and outcome could be nonlinear. Lowess is a widely used statistical method for estimating local regression surfaces to remove noise from raw data and clarify graphical presentations (16).

Third, we constructed a multivariable logistic regression model to investigate the association between ED-LOS and 28-day mortality, adjusting for the following covariates: patient demographics (age, sex, and race/ethnicity), initial vital signs, the counts of SIRS qualifying categories at ED arrival, initial laboratory data at least 24 hours after ICU admission (sodium, potassium, lactate, BUN, creatinine, WBC, hemoglobin, and platelet count), the maximum SOFA score within 24 hours of ICU admission. Furthermore, we repeated the logistic regression analysis after categorizing all patients into ED-LOS quartiles to identify the optimal ED-LOS.

All analyses were conducted using Google BigQuery, Python version 3.8.8, and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). A *p value* of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

We identified 1,849 patients eligible for analysis. **Table 1** showed summary statistics of all patients and each patient in the ED-LOS quartiles. The median (IQR)

TABLE 1.

Characteristics of All Patients and Patients Divided Into Quartiles Based on the Time From Emergency Department Visit to ICU Admission

Variables	Overall (*n* = 1,849)	< 3.3 hr (*n* = 466)	3.3–4.5 hr *n* = 459)	4.6–6.1 hr (*n* = 462)	> 6.1 hr (*n* = 462)
Patient demographics					
Age (yr), median (IQR)	68 (57–80)	68 (57–80)	67 (57–81)	68 (58–80)	67 (57–78)
Male, *n* (%)	1025 (55)	265 (57)	268 (58)	251 (54)	241 (52)
BMI (kg/m^2), median (IQR)	26.6 (23.4–30.9)	26.3 (22.8–29.8)	27.0 (23.6–31.1)	26.6 (23.5–31.0)	26.7 (23.6–32.1)
Race, *n* (%)					
Non-Hispanic White	1,244 (67)	317 (68)	313 (68)	301 (65)	313 (68)
Non-Hispanic Black	286 (15)	70 (15)	66 (14)	78 (17)	72 (16)
Hispanic	91 (5)	15 (3)	24 (5)	27 (6)	25 (5)
Triage vital signs, median (IQR)					
Systolic blood pressure (mm Hg)	113 (94–132)	116 (97–134)	112 (95–132)	113 (93–131)	110 (93–132)
Diastolic blood pressure (mm Hg)	64 (52–76)	67 (53–78)	64 (53–75)	63 (51–76)	63 (52–76)
Heart rate (/min)	99 (82–115)	100 (84–116)	97 (80–116)	98 (80–114)	99 (82–113)
Respiratory rate (/min)	20 (18–24)	20 (18–26)	20 (18–24)	19 (18–23)	18 (16–22)
Body temperature (°C)	36.9 (36.5–37.4)	36.9 (36.6–37.4)	36.9 (36.5–37.4)	36.9 (36.4–37.5)	36.9 (36.4–37.4)
First laboratory results, median (IQR)					
Sodium (mEq/L)	138 (134–141)	138 (135–141)	138 (134–141)	138 (134–141)	138 (134–141)
Potassium (mEq/L)	4.1 (3.7–4.7)	4.1 (3.8–4.7)	4.1 (3.7–4.6)	4.1 (3.6–4.7)	4.1 (3.6–4.7)
Lactate (mmol/L)	2.3 (1.6–3.3)	2.2 (1.6–3.2)	2.2 (1.5–3.1)	2.3 (1.6–3.4)	2.3 (1.6–3.4)
Blood urea nitrogen (mg/dL)	27 (17–46)	27 (17–46)	29 (18–50)	27 (17–45)	27 (16–45)
Creatinine (mg/dL)	1.2 (0.8–2.1)	1.1 (0.8–1.9)	1.2 (0.8–2.3)	1.3 (0.8–2.0)	1.2 (0.8–2.1)
WBC (10^3/μL)	10.6 (6.9–15.5)	10.8 (7.0–15.2)	10.6 (6.8–15.3)	10.0 (6.7–15.2)	10.8 (6.7–15.9)
Hemoglobin (mg/dL)	10.0 (8.5–11.6)	9.9 (8.4–11.5)	10.0 (8.6–11.5)	10.1 (8.5–11.7)	9.9 (8.4–11.7)
Platelet (10^3/μL)	177 (115–253)	177 (110–262)	169 (119–250)	179 (115–249)	177 (109–253)
Clinical scores, median (IQR)					
The counts of SIRS	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
SOFA score	6 (4–8)	6 (4–8)	6 (4–9)	6 (4–9)	6 (4–8)
Time from ED visit to ICU admission (hour), median (IQR)	4.6 (3.3–6.1)	2.6 (2.1–3.0)	3.9 (3.7–4.3)	5.3 (4.9–5.6)	7.1 (6.5–7.8)
Disposition					
28-d mortality, *n* (%)	258 (14)	59 (13)	73 (16)	68 (15)	58 (13)

ED = emergency department, IQR = interquartile range, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

age of overall patients was 68 (57–80) years, and 1,025 (55%) were male; 1,244 (67%) were non-Hispanic White, 286 (15%) were non-Hispanic Black, and 91 (5%) were Hispanic. The median (IQR) lactate level at least 24 hours after ICU admission and maximum SOFA score within 24 hours of ICU admission were 2.3 mmol/L (1.6–3.3) and 6 (4–8), respectively. The median ED-LOS was 4.6 (3.3–6.1) hours, and 258 (14%) died within 28 days of the ED visit. All patients were divided based on ED-LOS quartiles (i.e., < 3.3 hr, 3.3–4.5 hr, 4.6–6.1 hr, and > 6.1 hr), but we did not find any clinically meaningful differences in prognostic parameters of sepsis (e.g., the lactate level, the count of the SIRS criteria qualified, and the SOFA score) and outcome (i.e., 28-d mortality) across each quartile group.

Association Between ED-LOS and 28-Day Mortality

The Lowess curve had a left-skewed distribution (**Fig. 2**), and patients who were immediately admitted to the ICU (e.g., ED-LOS of < 2 hr) tended to have a higher 28-day mortality rate.

In the multivariable logistic regression model using ED-LOS as a continuous variable, ED-LOS was not significantly associated with 28-day mortality (adjusted odds ratio [OR] per hour increase, 1.04; 95% CI, 0.96–1.13; $p = 0.30$). However, as shown in **Figure 3**, patients in the higher time quartiles had higher 28-day mortality compared with those in the lowest time quartile (< 3.3 hr) (e.g., adjusted OR for patients in the second time quartile [3.3–4.5 hr], 1.59; 95% CI, 1.03–2.46; $p = 0.04$).

DISCUSSION

Using the data on 1,849 patients with sepsis from the MIMIC-IV and MIMIC-IV-ED databases, we found that patients in the lowest ED-LOS quartile (< 3.3 hr) had lower 28-day mortality than those in the higher ED-LOS quartiles (> 3.3 hr).

To our knowledge, this is the first study to statistically ascertain the optimal ED-LOS within 6 hours for patients with sepsis for whom compliance with the sepsis bundle is required. Patients in the lowest ED-LOS quartile (< 3.3 hr) were likely to have higher crude mortality but were significantly associated with lower mortality than those in the higher ED-LOS quartiles after adjustment for prognostic factors of sepsis. Therefore, immediate admission to the ICU to comply with the sepsis bundle may be effective in improving the prognosis of sepsis. Our findings suggest that a more immediate ICU admission (e.g., 3 hr) than 6 hours may be preferable as the target ED-LOS, which is consistent with the findings reported by Groenland et al (7). and Chalfin et al (8) in critically-ill patients that ICU admission within 2.4 hours and 3 hours were significantly associated with better outcomes, respectively.

Actually, there are conflicting findings as to whether ICU admissions within 6 hours of ED visits are associated with better prognostic outcomes among patients with sepsis (10, 11). Although Angstin et al and Zhang et al (10, 11) came to different conclusions from their own results, both studies reported higher mortality risk in patients with an ED-LOS of greater than or equal to 6 hours than those with an ED-LOS of less than 6 hours using adjusted logistic regression models. On top of this, considering our findings that patients who were admitted to the ICU within 3.3 hours tended to have a lower, although not significant, mortality rate than those who were admitted to the ICU within greater than 6.1 hours, it may be more beneficial to transfer patients to the ICU promptly after initial assessment and treatment at the ED, rather than necessarily using 6 hours as an optimal target.

Longer ED-LOS could be largely attributed to the lack of admitting beds resulting in the boarding of critically-ill patients in the ED, a critical issue that needs to be resolved (5, 17). However, given that the median ED-LOS of critically-ill patients in the United States was shorter than 6 hours (79 min [IQR, 36–145] in the general population and 197 min [IQR, 112–313] in mechanically ventilated patients) (18, 19), 3-hour target from ED visit to ICU admission of patients with sepsis requiring intensive care is feasible. Therefore, if medical resources permit, ICU admission within 3 hours of the ED visits may be beneficial in improving the prognosis of sepsis.

Our study has several limitations. First, the database used in this study covers patients enrolled from 2011 to 2019, suggesting that care for these patients may not have strictly adhered to the sepsis bundle proposed in SSCG 2021. Second, we considered patients with suspected infection and a SOFA score of 2 or greater upon ICU admission to be patients with sepsis according to previous studies using retrospective cohorts (20–22).

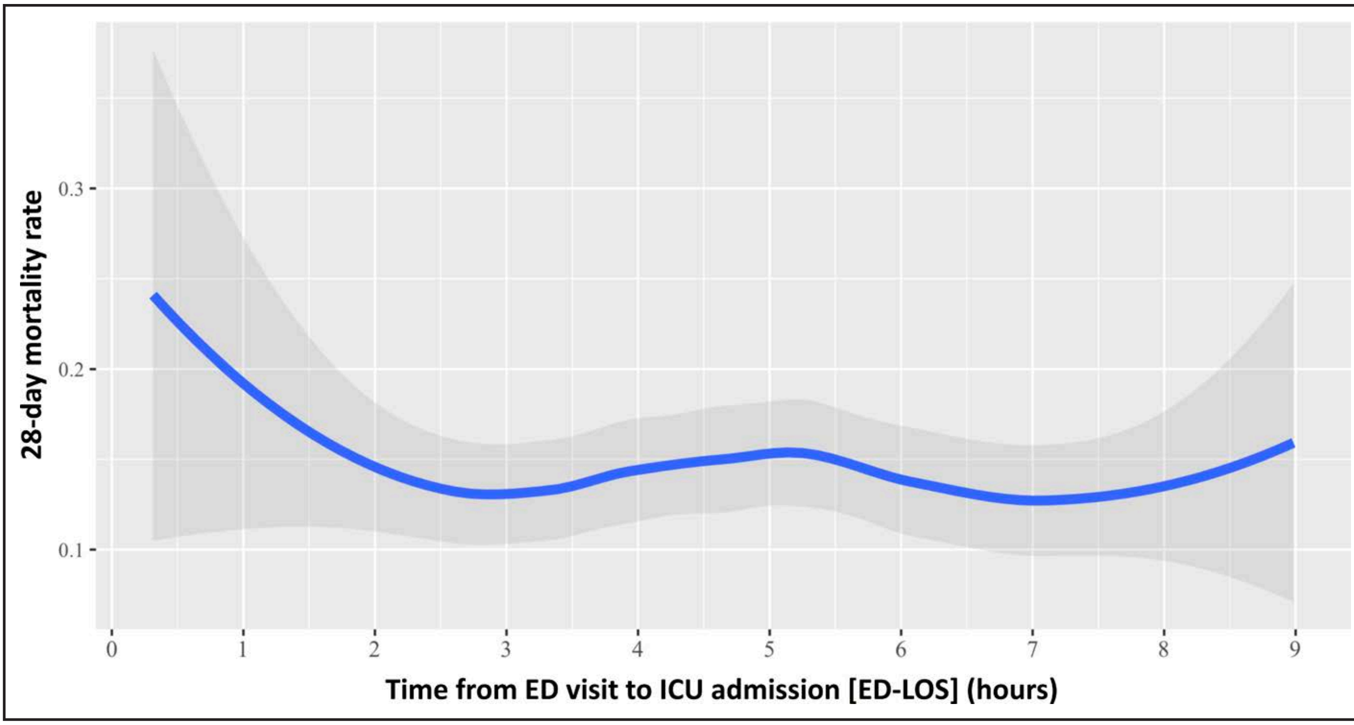

Figure 2. Association between time from ED visit to ICU admission and 28-day mortality using a locally weighted scatterplot smoother curve. We depicted the association between time from ED visit to ICU admission (i.e., ED length of stay [ED-LOS]) and 28-day mortality using a locally weighted scatterplot smoother (Lowess) curve. The blue line in the graph shows the estimated regression curve and the gray interval shows the 95% CI. ED-LOS = ED length of stay, ED = emergency department.

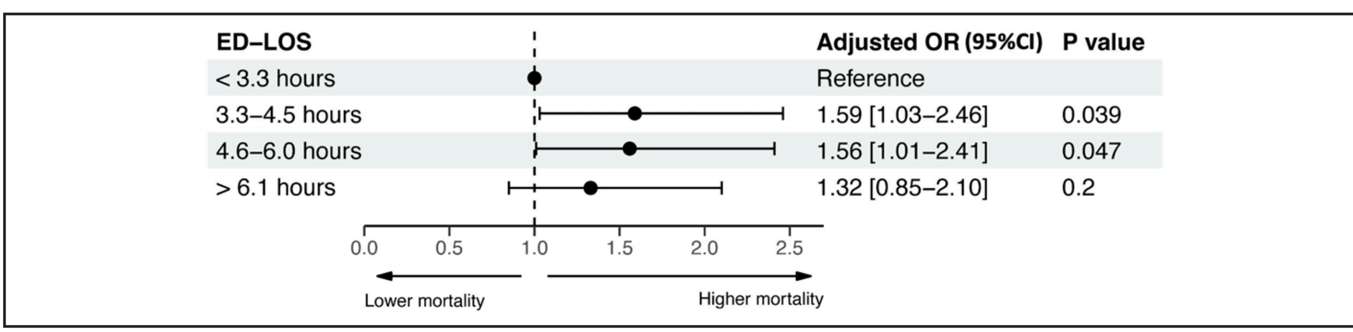

Figure 3. Associations between time from ED visit to ICU admission and 28-day mortality using multivariable logistic regression. We examined the association between time from ED visit to ICU admission (i.e., ED length of stay [ED-LOS]) and 28-day mortality using a multivariable logistic regression model. Points and error bars indicate the adjusted OR and 95% CI, respectively, with <3.3 hr from ED visit to ICU admission as the reference. ED-LOS = ED length of stay, ED = emergency department; OR = odds ratio.

However, this may have led to misclassification. Third, we had missing data on vital signs and laboratory parameters of patients eligible for analysis, which could be a potential source of bias. However, we believe this issue was minimized by using random forest imputation after excluding patients whose vital signs or laboratory data were all missing (23). In addition, the outcome measure used in this study, 28-day mortality, was limited to in-hospital mortality; we were unable to track patient outcomes after transfer or discharge from the ED to home. Fourth, because of the limited data available in the MIMIC-IV and MIMIC-IV-ED databases, we were not able to obtain data on medical interventions (e.g., administration of antibiotics, the performance of imaging tests) and changes in vital signs over time in the ED, which may be a source of confounding bias. In addition, we could not fully investigate the mechanism of the association between ED-LOS and the 28-day mortality rate in our study. These issues should be addressed in future prospective studies. These issues should be addressed in future prospective studies. Fifth, our study was not preregistered in an authorized clinical trial registry (e.g., UMIN-CTR), but our study protocol was approved by an institutional review board. Finally, the databases we used in this study are from a single center in the United States, which may limit the generalizability of our results. To verify our findings, multicenter studies including a variety of geographic areas (e.g., hospitals in rural areas or outside the United States) are warranted to consider differences in-hospital care systems.

CONCLUSIONS

Earlier admission to the ICU (e.g., within 3 hr of ED visits) was associated with lower 28-day mortality in patients with sepsis. For patients with sepsis who require intensive care, a more immediate ICU admission than 6 hours may result in better patient outcomes.

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Drs. Shibata and Osawa equally contributed to this article.

Drs. Shibata, Osawa, and Goto conceived and designed the study. Drs. Shibata, Osawa, and Fukuchi performed the statistical analyses. Drs. Shibata and Osawa drafted the initial article. Dr. Goto supervised the study. All authors interpreted the data, critically revised the article for important intellectual content, and approved the final article.

The authors have disclosed that they do not have any potential conflicts of interest.

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Given that the clinical data used for this research was obtained from the Medical Information Mart for Intensive Care Emergency Department and the Medical Information Mart for Intensive Care databases, publicly available and de-identified databases based on the HIPAA Safe Harbor provision, the TXP Medical Ethical Review Board waived the requirement for the ethical approval statement and informed consent (TXPREC-008).

The Medical Information Mart for Intensive Care Emergency Department (MIMIC-IV-ED) dataset version 2.2 is an extensive, publicly available database consisting of de-identified health-related data at the ED. Information on how to access the MIMIC-IV-ED database is found at https://physionet.org/content/mimic-iv-ed/2.2/. The Medical Information Mart for Intensive Care IV (MIMIC-IV) dataset version 2.2 is a large publicly available dataset consisting of de-identified health-related data in the ICU. Information on how to access the MIMIC-IV database is found at https://physionet.org/content/mimiciv/2.2/.

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