TIME FROM HOSPITAL ADMISSION TO ONSET OF SEPTIC SHOCK IS ASSOCIATED WITH HIGHER IN-HOSPITAL MORTALITY

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ABSTRACT—Objective: Several studies have shown septic shock developing later during the hospital stay is associated with higher mortality. However, the precise point at which time from hospital admission to the onset of septic shock (admission-shock-onset-time) becomes an independent prognostic marker of mortality remains unknown. This study evaluated the association between admission-shock-onset-time and in-hospital mortality among patients with septic shock and the optimal cutoff period to categorize early- and late-onset septic shock. Method: We conducted a single-center retrospective, observational cohort study at a quaternary care academic hospital comprising adult patients with septic shock admitted to a medical intensive care unit (ICU) from January 2011 to December 2020. A multivariable additive logistic regression model was developed to assess if log-transformed admission-shock-onset-time was associated with in-hospital mortality. The thin plate spline function was used to describe the nonlinear relationship between the log-transformed admission-shock-onset-time and in-hospital mortality. The primary outcome was in-hospital mortality, and the secondary outcome was ICU mortality. Results: Two thousand five hundred twenty patients met the inclusion criteria with an overall in-hospital mortality of 37.3%. The log-transformed admission-shock-onset-time was associated with higher in-hospital and ICU mortality even after adjusting for clinical variables. The odds ratio for in-hospital mortality continued to increase throughout the observation period. The adjusted odds ratio exceeded 2 in between 20.1 and 54.6 h, and it surpassed 3 in between 54.6 and 148.4 h of the time from the hospital admission to shock onset. Conclusion: In-hospital mortality continued to rise as admission-shock-onset-time increased in patients with septic shock. No clear dichotomization between early and late septic shock could be ascertained, and this categorization may limit our understanding of the temporal relationship of shock onset to mortality.

KEYWORDS—Hospital-onset; late onset; outcomes; sepsis; septic shock

ABBREVIATIONS—APACHE III — Acute Physiology And Chronic Health Evaluation III; CI — confidence interval; COPD — chronic obstructive lung disease; ICU — intensive care unit; IQR — interquartile range; IRB — institutional review board; OR — odds ratio

INTRODUCTION

Septic shock is characterized by a dysregulated immune response triggered by an infection that requires vasopressor support to maintain systemic circulation (1–3). This remains a significant cause of health loss worldwide, with an overall mortality approaching 40% to 60% (4). National and international committees have prioritized efforts to improve outcomes in sepsis by promoting early recognition and implementation of standardized therapeutic protocols (5,6). However, current 3- and 6-h bundles for sepsis management have primarily been developed from studies conducted on patients presenting to emergency departments with sepsis (7,8). Patients developing sepsis and septic shock during their hospital stay have higher mortality compared with those who presented to the emergency department with sepsis (9–11).

Previous studies with small cohorts found that patients with late-onset septic shock (the onset of shock 24 or 48 h after the intensive care unit [ICU] admission) had higher mortality than early-onset septic shock (12–14). These studies have thus proposed that the development of shock beyond the initial 48 h therefore plays an independent prognostic role in outcomes in septic shock. This arbitrary dichotomization of time at 24 to 48 h implies a change in either patient or disease characteristics at the aforementioned time period with the associated difference in outcome in the latter group. It also erroneously means that an increase in mortality associated with late-onset sepsis and septic shock is static. The primary objective of this study was to evaluate the temporal relationship between septic shock onset from hospital...
admission (admission-shock-onset-time) and its association with in-hospital mortality in a larger cohort of patients with septic shock. We also aimed to determine if an optimal cutoff time period can distinguish early- and late-onset septic shock.

**METHODS**

We conducted a single-center, retrospective cohort study comprising adult patients with septic shock admitted to the medical ICU at a large quaternary academic center between January 1, 2011, and December 31, 2020. Exclusion criteria included patients younger than 18 years, patients with sepsis but without septic shock, and patients transferred from other hospitals’ ICU or general wards where hospital admission date and time cannot be determined accurately. Patients transferred directly from other hospitals’ emergency departments to our medical ICU were included in this study. In cases of repeated admissions during the study period, only the first episode of sepsis or septic shock was included in the analysis. All clinical data were gathered from electronic medical records.

The 2001 American College of Chest Physicians/Society of Critical Care Medicine consensus criteria were used to define sepsis and septic shock. Septic shock was defined as all of the following: (i) a suspected or proven infection, (ii) at least two criteria of systemic inflammatory response syndrome, and (iii) an acute circulatory failure requiring vasopressor support (15). We manually collected the confirmed or presumed source of infection from documentations such as history and physical examination and progress notes. The common practice at our facility involves the initiation of vasopressors after adequate volume resuscitation to achieve a MAP of ≥65 mm Hg. However, given the retrospective nature of this study, the specific rationale for vasopressor initiation was at the discretion of individual providers. Admission-shock-onset-time was defined as the duration from the hospital admission to the initiation of continuous vasopressor infusion (either norepinephrine, vasopressin, epinephrine, or phenylephrine). The primary outcome was admission-shock-onset-time and in-hospital mortality. The secondary outcome was admission-shock-onset-time and ICU mortality.

Patients’ characteristics were described using the sample median with interquartile range (IQR: 25th and 75th percentiles) for continuous variables and the number with proportion for categorical variables. Missing values were imputed using the MissForest package, an iterative nonparametric imputation method based on a random forest (16). It fits a random forest on the observed part and then predicts the missing piece by performing multiple imputation schemes by averaging over many unpruned classification or regression trees. The admission-shock-onset-time was log-transformed to produce symmetric distribution for further statistical analysis.

We defined the patients’ survival rate as the number of survivors within every 12 h of the admission-shock-onset-time (the numerator) as a proportion of the total number of patients at risk at the time period (the denominator). Poisson regression was applied to study the association between the admission-shock-onset-time and the patients’ survival rate. This modeling method allowed us to examine whether there is a statistical difference in survival rate among different admission-to-shock-onset times.

A multivariable additive logistic regression analysis was performed to calculate the odds ratio (OR) of in-hospital mortality. The logistic regression model was adjusted based on *a priori* determined variables: age, sex, Acute Physiology And...
A total of 2,520 patients with septic shock were included in the analysis, as shown in Figure 1. The study population included 1,139 females (45.2%), with the median age and APACHE III score being 64 years (IQR, 55–72 years) and 93 years (IQR, 74–116 years), respectively. Patients’ baseline characteristics, characteristics at ICU admission, and outcomes are shown in Table 1. Of these, 51.7% of patients were directly admitted to ICU from the emergency department. In comparison, 40.5% were transferred from general wards, 0.3% were from long-term care facilities, and 7.5% were from other admitting sources; 19.5% of patients developed acute kidney injury, whereas 46.9% of patients required invasive mechanical ventilation during their stay in ICU. Intensive care

### Baseline and characteristics on MICU admission

| Factors                        | OR for in-hospital mortality | 95% CI        | P     |
|-------------------------------|------------------------------|---------------|-------|
| Maximum lactate in 24 h of shock-recognition time | —                            | —             | <0.001|
| Total bolus i.v. fluid administration in 24 h of shock-recognition time, mL | 1.441 (591–3,383)            |               |       |
| Total i.v. fluid administration in 24 h of shock-recognition time, mL | 5.046 (2,445–9,147)          |               |       |
| Patient received CMS-approved antibiotics prior to shock-onset time | 2.103 (83.2%)                |               |       |
| Time from shock-onset time to antibiotic administration, min | —330 (—1,170 to —30)        |               |       |
| Maximum norepinephrine dose in 24 h of shock-onset time | 20.0 (10.0–50.0)             |               |       |

### Baseline characteristics

| Factors                        | OR for ICU mortality | 95% CI        | P     |
|-------------------------------|----------------------|---------------|-------|
| Maximum lactate in 24 h of shock, mmol/L | 1.06                | 1.03–1.04     | <0.001|
| Maximum NE equivalent dose in 24 h of shock, μg/min | 1.03                | 1.03–1.04     | <0.001|
| Total i.v. fluid administration in 24 h of shock, mL | 1.00                | 1.00–1.00     | 0.878 |
| Time from shock to antibiotics time | 1.00                | 1.00–1.00     | 0.267 |

### Multivariable additive logistic regression analyses for in-hospital mortality and ICU mortality

### RESULTS

A total of 2,520 patients with septic shock were included in the analysis, as shown in Figure 1. The study population included 1,139 females (45.2%), with the median age and APACHE III score being 64 years (IQR, 55–72 years) and 93 years (IQR, 74–116 years), respectively. Patients’ baseline characteristics, characteristics at ICU admission, and outcomes are shown in Table 1. Of these, 51.7% of patients were directly admitted to ICU from the emergency department. In comparison, 40.5% were transferred from general wards, 0.3% were from long-term care facilities, and 7.5% were from other admitting sources; 19.5% of patients developed acute kidney injury, whereas 46.9% of patients required invasive mechanical ventilation during their stay in ICU. Intensive care

### Baseline and characteristics on MICU admission

| Age, y | 64 (55–72) |
| Female | 1,139/2,520 (45.2%) |
| Chronic dialysis | 378/2,520 (15.0%) |
| Cirrhosis | 394/2,520 (15.6%) |
| COPD | 606/2,520 (24.0%) |
| Diabetes | 759/2,520 (30.1%) |
| Immune suppression | 835/2,520 (33.1%) |
| Malignancy | 718/2,520 (28.5%) |

### Characteristics on ICU admission

#### Admission to the medical ICU from

- Emergency department | 1,304/2,520 (51.7%)
- General wards | 1,021/2,520 (40.5%)
- Others | 188/2,520 (7.8%)

#### Source of Infection

- Chronic Health Evaluation (APACHE) III: history of chronic dialysis, cirrhosis, chronic obstructive lung disease, diabetes, immunosuppression, history of malignancy, maximum lactate level within 24 h of shock onset, peak dose of norepinephrine equivalent dose within 24 h of septic shock (17), total i.v. fluid administration within 24 h of septic shock, and time from septic shock to antibiotic administration. These variables were selected to adjust for the severity of septic shock and interventions known to alter outcomes in patients with septic shock to analyze the impact of admission-shock-onset-time on in-hospital mortality. We used a four-knot restricted cubic spline function to allow for the possibility of a nonlinear relationship between log-transformed admission-shock-onset-time and mortality (18). The adjusted OR curve of the log-transformed admission-shock-onset-time for in-hospital mortality was constructed using an additive logistic regression model with the baseline adjusted OR set at 1 h of admission-shock-onset-time (zero in the log scale of the time) (19,20). All analyses were performed using the R software program (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.4; The SAS Institute, Cary, NC). The level of statistical significance was set at P < 0.05 (two-tailed). This study was approved by Cleveland Clinic Institutional Review Board (IRB 15-1233).
unit mortality was 29.5%, and the overall in-hospital mortality was 37.3%. Most patients who survived were discharged home or to skilled nursing facilities (Table 1). Numbers of missing values that were imputed in the further analyses in this study are shown in Supplemental Figure 1, http://links.lww.com/SHK/B493. The histograms of admission-shock-onset time and the log-transformed admission-shock-onset-time are shown in Supplemental Figure 2, http://links.lww.com/SHK/B493.

Comparisons of likelihoods of in-hospital death according to every 12-h intervals showed no significant differences when comparing two sequential time intervals (Supplemental Tables 1, 2, and 3, and Supplemental Fig. 3, http://links.lww.com/SHK/B493). We were unable to identify a distinct time interval, which could discriminate early- from late-onset septic shock. Hence, we proceeded with admission-shock-onset-time as a continuous variable.

The multivariable additive logistic regression analyses for in-hospital mortality and ICU mortality are shown in Table 2. The adjusted OR curve of the log-transformed admission-shock-onset-time for in-hospital mortality based on the additive logistic regression model is shown in Figure 2. In this model, the baseline adjusted OR was set at 1 h of admission-shock-onset-time (zero in the log scale of the time). The OR for in-hospital mortality continuously increased as admission-shock-onset-time increased in the observed period. As shown in Figure 2, the adjusted OR exceeded 2 in between 20.1 and 54.6 h of the time from the hospital admission to shock onset. The adjusted OR exceeded 3 in between 54.6 and 148.4 h of the time from the hospital admission to shock onset.

The adjusted OR curve of the log-transformed admission-shock-onset-time for ICU mortality based on the additive logistic regression model is shown in Figure 3. The adjusted OR curves of the log-transformed admission-shock-onset-time admitted to the medical ICU from the emergency department and non-emergency department (hospital wards) showed a similar association between in-hospital mortality and admission-shock-onset-time (Supplemental Figs. 4 and 5, http://links.lww.com/SHK/B493).

**DISCUSSION**

This study demonstrates that in-hospital mortality increases as admission-shock-onset-time increases in patients with sepsis even after adjusting for comorbidities and baseline illness severity. Our study confirms that the timing of shock onset in patients with sepsis during their hospital stay is independently associated with increased in-hospital mortality. But more importantly, we illustrated that the association between the timing of shock onset and in-hospital mortality is continuous without clear inflection points, and there is a linear relationship between mortality and the time to shock onset during their stay in the hospital.

Our study is the first study to describe the temporal relationship between time to shock onset and mortality in sepsis. In previous studies, 24 and 48 h from admission to ICU were used as arbitrary cutoffs to dichotomize septic patients into early- and late-onset septic...
The mortality rate was 1.5 to 2 times higher in late-onset septic shock (12–14). The arbitrary dichotomization of time at 24 to 48 h implies a change in either patient or disease characteristics at the aforementioned time periods driving the higher mortality in the latter group (21). Our study found that mortality increased continuously with time to onset of septic shock from hospital admission, implying that mortality associated with this time duration is not a static phenomenon. Other authors have shown the onset of sepsis later during the hospital stay, defined with terms such as hospital-onset sepsis to be associated with higher mortality compared with community-acquired sepsis or septic shock (9,10). In our subgroup analysis, we found a similar temporal relationship of in-hospital mortality to the onset of septic shock both in patients admitted to ICU with septic shock directly from the emergency department or other admitting sources confirming that time to onset of septic shock is independently associated with mortality irrespective of where the patient is cared for at septic shock onset.

The higher mortality in septic shock developing later in hospital stay is likely multifactorial. Previous studies have shown the process of care variables, including delays in recognition, antibiotic administration, i.v. fluid administration, and nonadherence to bundled care and vasoactive support, may be responsible for an increase in mortality in septic shock (12,22–24). Patient-specific characteristics, including severe comorbidities, underlying debilitation, and the development of organ dysfunction during the hospital course, also may play a significant role in driving this mortality. A more extended hospital stay also puts this patient population at high risk of developing hospital-acquired infections with antibiotic-resistant organisms, which are associated with higher rates of mortality (25–27). By considering the time to onset of septic shock as a continuous variable, future studies can inform the specific mechanisms that contribute to this phenomenon.

The most apparent strength of this study is that this is the largest cohort of patients who have been assessed to study outcomes of sepsis based on the timing of septic shock onset (12–14). In addition, to the best of our knowledge, this is the first study to suggest that the relationship between time to shock onset and mortality does not support the dichotomization of septic shock into “early” and “late.” A previous study using two large national databases reported that patients with initially less severe sepsis made up the majority of sepsis-related deaths, whereas most performance improvement efforts have been focused on the most severely ill patients (28). Our study also supports the importance of future research to identify patients at high risk of developing septic shock later on in their hospitalization and to identify and develop interventions to prevent the development of septic shock in this cohort.

We acknowledge that this study has limitations mainly resulting from its single-center, retrospective nature and reliance on electronic medical record documentation. We performed multivariable analyses adjusting all known or suspected confounders to account for the inevitable risk of residual confounding. We also performed multiple imputations for missing values and ran subgroup analysis for a priori identified variables. Because this study was not designed to determine the reason for the delay in

![Adjusted Odds ratio for ICU mortality](image-url)
vasopressors, a delay in recognition of shock or uncertainty in initiation of vasopressors by the bedside clinician might have resulted in residual confounding. However, we performed multivariable analyses adjusting for all known or suspected confounders and subgroup assessment showcasing similar trends. Therefore, we believe that the continuous nature of the relationship between admission-shock-onset-time and mortality is still likely to be the case despite these limitations. Second, we could not obtain the information on causative pathogens, which might have affected mortality (25). Future analyses should evaluate the change in microbiology patterns in this group of patients and their association with mortality.

## CONCLUSION

In this study, we demonstrated that the time to onset of septic shock was independently associated with in-hospital mortality. We also showed in-hospital mortality increased continuously and without dichotomization points as the time from hospital admission-shock-onset-time increased in patients with septic shock. Continued study is needed to identify the specific mechanisms responsible for this relationship to develop appropriate identification and management strategies in this patient population.

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