# Time From Hospital Admission to Onset of Septic Shock is Associated with Higher In-Hospital Mortality

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**Research Article**

# Abstract

## Objective:

Several studies have shown septic shock developing later during the hospital stay are associated with greater 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 aimed to evaluate the association between admission-shock-onset-time and in-hospital mortality among patients with septic shock, as well as the optimal cut-off time period to categorize early and late-onset septic shock.

## Method:

We conducted a single-center retrospective, observational cohort study at a quaternary academic hospital comprising adult patients with septic shock admitted to a medical intensive care unit (ICU) from 01/2011 to 12/2020. A multivariable Cox regression model was developed to assess if log-transformed admission-shock-onset-time was associated with in-hospital mortality. A multivariable additive logistic regression was performed to estimate the odds ratio for mortality using the log-transformed admission-shock-onset-time. 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:

A total of 2,520 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 mortality [Hazard ratio (HR): 1.08, 95% confidence interval (CI): 1.05-1.11, p< 0.001] and ICU mortality (HR: 1.06, 95%CI: 1.03-1.10, p<0.001). This association remained significant after adjusting for clinical variables. The odds ratio for in-hospital mortality continued to increase throughout the observation period.

## Conclusion:

In-hospital mortality continued to rise as admission-shock-onset-time increased in septic shock. No clear dichotomization between early and late septic shock can be ascertained and this categorization may limit our understanding of the temporal relationship of shock onset to mortality.

## Trial Registration

This study was approved by Cleveland Clinic Institutional Review Board (IRB 15-1233).

# Background

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 major cause of health loss worldwide with an overall mortality approaching 40–60% [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-hour bundles for sepsis management have largely 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 to those who presented to the emergency department with sepsis [9–11].

Previous studies with small cohorts found patients with late-onset septic shock (defined as the onset of shock 24 hours or 48 hours 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 hours thus plays an independent prognostic role in outcomes in septic shock. This arbitrary dichotomization of time at 24–48 hours 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 implies 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 of septic shock-onset from hospital admission (admission-shock-onset-time) and its association to in-hospital mortality in a larger cohort of patients with septic shock. We also aimed to determine if an optimal cut-off time period can distinguish early and late-onset septic shock.

## Methods

We conducted a single-center, retrospective cohort study comprising of adult patients with septic shock who were admitted to the medical ICU at a large quaternary academic center between January 1, 2011, and December 31, 2020. Exclusion criteria included patients less than 18 years old, patients with sepsis but without septic shock, and patients transferred from other hospitals' ICU or general ward 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, (iii) an acute circulatory failure requiring vasopressor support [15]. The common practice at our facility involves the initiation of vasopressors after adequate volume resuscitation to achieve mean arterial blood pressure 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 time of initiation of vasopressor continuous infusion (either norepinephrine, vasopressin, epinephrine, or phenylephrine). Primary outcome was admission-shock-

onset-time and in-hospital mortality. Secondary outcome was admission-shock-onset-time and ICU mortality.

We performed statistical analysis using R version 4.1.3 software (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute, Inc.). Patients' characteristics were summarized by a median with interquartile range (IQR: 25th and 75th percentiles) for continuous variables. Frequencies and percentages were shown for categorical variables. We described the Poisson distribution of admission-shock-onset-time and the fraction of survival based on each time interval (every 1 hour and every 12 hours bin). Then, we compared two sequential time intervals to evaluate for any significant differences between each sequential time interval. We initially planned to use that as a cutoff to divide the admission-shock-onset-time into early-onset and late-onset if there were any significant differences. If there were not any such time intervals, we planned to use admission-shock-onset-time as a continuous variable. A multivariable Cox regression analysis with log transformation of admission-shock-onset-time was performed to calculate the hazard ratio (HR) of in-hospital mortality. The Cox regression model was adjusted based on *a priori* determined variables: age, sex, Acute Physiology And Chronic Health Evaluation (APACHE) III, history of chronic dialysis, cirrhosis, chronic obstructive lung disease (COPD), diabetes, immunosuppression, history of malignancy, maximum lactate level within 24 hours of shock onset, peak dose of norepinephrine equivalent dose within 24 hours of septic shock [16], total intravenous fluid administration within 24 hours of septic shock and time from septic shock to antibiotics administration. Missing values were imputed using the MissForest package, which is an iterative nonparametric imputation method based on a random forest [17]. It fits a random forest on the observed part and then predicts the missing part performing multiple imputation schemes by averaging over many unpruned classification or regression trees. A multivariable additive logistic regression was performed to estimate the odds ratio smooth function for the log-transformed admission-shock-onset-time [18]. The thin plate spline function was used for the nonlinear function of the log-transformed admission-shock-onset-time. This study was approved by Cleveland Clinic Institutional Review Board (IRB 15-1233). In view of the retrospective nature of the study, the IRB waived the need for written informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Results

A total of 2,520 patients with septic shock were included in the analysis, as shown in Fig. 1. The study population included 1,139 females (45.2%), with the median age and APACHE III score being 64 years (IQR: 55–72) and 93 (IQR: 74–116), 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 while 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, while 46.9% of patients required invasive mechanical ventilation during their stay in ICU. ICU 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).

## Table 1
## Baseline and After-MICU admission characteristics.

| Baseline characteristics | |
|---|---|
| Age (Years) | 64 (55–72) |
| Female | 1,139 / 2,520 (45.2%) |
| BMI (Kg/m$^{2)}$) | 27.3 (23.0–33.0) |
| Chronic dialysis | 378 / 2,520 (15.0%) |
| Cirrhosis | 394 / 2,520 (15.6%) |
| COPD | 606 / 2,52 (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 | 1,304 / 2,520 (51.7%) |
| Emergency department | 1,021 / 2,520 (40.5%) |
| General wards | 188 / 2,520 (7.8%) |
| Others | |
| APACHE III | 93 (74–116) |

| |
|---|
| BMI: body mass index |
| COPD: chronic obstructive pulmonary disease |
| APACHE: acute physiology and chronic health evaluation |
| IVF: intravenous fluid |
| CMS: Centers for Medicare and Medicaid |
| ICU: intensive care unit |

| Baseline characteristics | |
| --- | --- |
| Source of Infection | 452 (17.9%) |
| Pulmonary | 239 (9.5%) |
| Urinary tract | 402 (16.0%) |
| Intra-abdominal | 128 (5.0%) |
| Soft tissue | 4 (0.2%) |
| Gynecology | 1,295 (51.4%) |
| Others | |
| Heart rate (beats/min) | 117 (100−133) |
| Mean arterial pressure (mmHg) | 53 (47−59) |
| Respiratory rate (/min) | 39 (32−47) |
| Temperature (C) | 36.6 (36.3−37.3) |
| White blood cell x 100 (/m$^3$) | 12.9 (5.5−21.2) |
| Max. Lactate in 24 hours shock-recognition time | 2.9 (1.6−5.5) |
| Total bolus IVF administration in 24 hours of shock-recognition time (ml) | 1441 (591−3383) |
| Total IVF administration in 24 hours of shock-recognition time (ml) | 5,046 (2,445-9,147) |
| Patient received CMS approved antibiotics prior to shock-onset time | 2,103 / 2,529 (83.2%) |
| Time from shock-onset time to antibiotics administration (min) | -330 (-1,170- -30) |
| Max norepinephrine dose in 24 hours of shock-onset time | 20.0 (10.0−50.0) |
| Outcomes | |
| In-hospital mortality | 940 / 2,520 (37.3%) |
| ICU-mortality | 743 / 2,520 (29.5%) |
| Acute Kidney Injury | 491 / 2,520 (19.5%) |

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| --- |
| BMI: body mass index |
| COPD: chronic obstructive pulmonary disease |
| APACHE: acute physiology and chronic health evaluation |
| IVF: intravenous fluid |
| CMS: Centers for Medicare and Medicaid |
| ICU: intensive care unit |

| Baseline characteristics | |
|---|---|
| Norepinephrine duration (days) | 1.67 (0.79−3.41) |
| Hospital free-days (days) | 0 (0-15.7) |
| ICU free-days (days) | 20.1 (0-24.4) |
| Need for Invasive mechanical ventilation | 1,188 / 2,520 (46.9%) |
| Duration of mechanical ventilation (days) | 2.0 (0.3−5.5) |
| Discharge destination among survivors (n = 1,582) | 578 / 1,580 (36.6%) |
| • Home | 225 /1,580 (14.2%) |
| • Long team acute care facility | 474 / 1,580 (30.0%) |
| • Skilled care facility | 56 / 1,580 (3.5%) |
| • Physical rehabilitation center | 223 / 1,580 (14.1%) |
| • Hospice | 24 / 1,580 (1.5%) |
| • Others | |
| BMI: body mass index | |
| COPD: chronic obstructive pulmonary disease | |
| APACHE: acute physiology and chronic health evaluation | |
| IVF: intravenous fluid | |
| CMS: Centers for Medicare and Medicaid | |
| ICU: intensive care unit | |

Comparisons of likelihoods of in-hospital death according to both every one-hour intervals and every 12 hours intervals showed no significant differences when comparing two sequential time intervals (**Supplementary File**). 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.

In the multivariable Cox regression model, the log-transformed admission-shock-onset-time was associated with higher in-hospital mortality (HR: 1.08, 95%CI: 1.05−1.11, p < 0.001) and ICU mortality (HR: 1.06, 95%CI: 1.03−1.10, p < 0.001), as shown in Table 2. The adjusted odds ratio curve of the log-transformed admission-shock-onset-time for in-hospital mortality based on the additive logistic regression model is shown in Fig. 2. In this model, the baseline adjusted odds ratio was set at 1 hour of admission-shock-onset-time (zero in the log scale of the time). The odds ratio for in-hospital mortality continued to increase throughout the observation period. The adjusted odds ratio curve of the log-

transformed admission-shock-onset-time for ICU mortality based on the additive logistic regression model is shown in Fig. 3. The adjusted odds ratio 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 to in-hospital mortality and admission-shock-onset-time. (Supplementary File ).

Table 2

Multivariable Cox regression analysis for in-hospital mortality and ICU-mortality.

| Factors | HR for in-hospital mortality | 95% CI | p-value |
|---|---|---|---|
| Log-transformed admission to shock-recognition time | 1.08 | 1.05–1.11 | < 0.001 |
| Age | 1.01 | 1.00–1.01 | 0.012 |
| Sex (Male) | 1.00 | 0.87–1.14 | 0.952 |
| APACHE III | 1.01 | 1.01–1.01 | < 0.001 |
| Chronic dialysis | 0.94 | 0.78–1.12 | 0.476 |
| Cirrhosis | 1.15 | 0.97–1.37 | 0.102 |
| COPD | 1.01 | 0.86–1.17 | 0.931 |
| Diabetes | 0.94 | 0.81–1.08 | 0.382 |
| Immune Suppression | 0.94 | 0.79–1.11 | 0.455 |
| Malignancy | 1.30 | 1.09–1.56 | 0.004 |
| Maximum lactate in 24 hours of shock (mmol/l) | 1.09 | 1.04–1.14 | 0.004 |
| Maximum NE equivalent dose in 24 hours of shock (mcg/min) | 2.35 | 2.17–2.54 | < 0.001 |
| Total IVF administration in 24 hours of shock (ml) | 0.78 | 0.72–0.84 | < 0.001 |

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|---|
| HR: hazard ratio |
| CI: confidence interval |
| APACHE: Acute Physiology And Chronic Health Evaluation |
| COPD: chronic obstructive lung disease |
| NE: norepinephrine |
| IVF: intravenous fluid |

| Factors | HR for in-hospital mortality | 95% CI | p-value |
|---|---|---|---|
| Time from shock to antibiotics time | 0.99 | 0.99–1.00 | 0.046 |

| Factors | HR for ICU mortality | 95% CI | p-value |
|---|---|---|---|
| Log-transformed admission to shock-recognition time | 1.06 | 1.03–1.10 | < 0.001 |
| Age | 1.00 | 0.99–1.01 | 0.419 |
| Sex (Male) | 1.00 | 0.86–1.16 | 0.990 |
| APACHE III | 1.01 | 1.01–1.02 | < 0.001 |
| Chronic dialysis | 0.85 | 0.68–1.04 | 0.120 |
| Cirrhosis | 1.05 | 0.87–1.26 | 0.647 |
| COPD | 1.02 | 0.86–1.21 | 0.813 |
| Diabetes | 1.02 | 0.86–1.20 | 0.803 |
| Immune Suppression | 0.99 | 0.82–1.20 | 0.954 |
| Malignancy | 1.15 | 0.94–1.40 | 0.177 |
| Maximum lactate in 24 hours of shock (mmol/l) | 1.18 | 1.12–1.25 | < 0.001 |
| Maximum NE equivalent dose in 24 hours of shock (mcg/min) | 2.21 | 2.01–2.42 | < 0.001 |

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|---|
| HR: hazard ratio |
| CI: confidence interval |
| APACHE: Acute Physiology And Chronic Health Evaluation |
| COPD: chronic obstructive lung disease |
| NE: norepinephrine |
| IVF: intravenous fluid |

| Factors | HR for in-hospital mortality | 95% CI | p-value |
|---|---|---|---|
| Total IVF administration in 24 hours of shock (ml) | 0.76 | 0.70−0.83 | < 0.001 |
| Time from shock to antibiotics time | 0.99 | 0.99−1.00 | 0.153 |
| HR: hazard ratio | | | |
| CI: confidence interval | | | |
| APACHE: Acute Physiology And Chronic Health Evaluation | | | |
| COPD: chronic obstructive lung disease | | | |
| NE: norepinephrine | | | |
| IVF: intravenous fluid | | | |

# Discussion

In this study, we demonstrate 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 in nature 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- hours from admission to ICU were used as arbitrary cut-offs to dichotomize septic patients into early-onset and late-onset septic shock showed the mortality rate to be 1.5 to 2 times higher in late-onset septic shock [12−14]. The arbitrary dichotomization of time at 24−48 hours implies a change in either patient or disease characteristics at the aforementioned time periods driving the higher mortality in the latter group [19]. In our study, we found mortality increased continuously with time to onset of septic shock from hospital admission implying thereby 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 in comparison to 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 from 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 the course of hospital stay is likely multifactorial. Previous studies have shown the process of care variables including delays in recognition, antibiotic administration, intravenous fluid administration, and non-adherence to bundled care and vasoactive support may be responsible for an increase in mortality in septic shock [12, 20–22]. Patient-specific characteristics including severe comorbidities, underlying debilitation, and the development of organ dysfunction during the hospital course also may play a major role in driving this mortality. A longer hospital stay also puts this patient population at high risk for developing hospital-acquired infections with antibiotic-resistant organisms, which are associated with higher rates of mortality [23–25]. By considering the time to onset of septic shock as a continuous variable, future studies can inform on the specific mechanisms that contribute to this phenomenon.

The most obvious strength of this study is that this is the largest cohort of patients that 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 while most performance improvement efforts have been focused on the most severely ill patients [26]. Our study also supports the importance of future research to identify patients at high risk for developing septic shock later on in the course of 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 which are mainly results of its single-center, retrospective nature and reliance on electronic medical record documentation. To account for the inevitable risk of residual confounding, we performed multivariable analyses adjusting all known or suspected confounders. We also performed multiple imputations for missing values and ran subgroup analysis for *a priori* identified variables. Since this study was not designed to identify the reason for the delay in vasopressors, a delay in recognition of shock or delay 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 finding that the continuous nature of the relationship between admission-shock-onset-time and mortality is still likely to be the case despite these limitations. Secondly, we could not obtain the information on causative pathogens which in turn might have affected mortality [23]. 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 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 in order to develop appropriate identification and management strategies in this patient population.

# Abbreviations List

ICU
intensive care unit
IQR
interquartile range
HR
hazard ratio
APACHE III
Acute Physiology And Chronic Health Evaluation III
COPD
chronic obstructive lung disease
IRB
Institutional Review Board

# Declarations

**Ethics approval and consent to participate:** This study was approved by Cleveland Clinic Institutional Review Board (IRB 15-1233) and waived the need for written informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent for publication:** Consent for publication was waived because the data did not include individual details.

**Competing interests:** AKK consults for Edwards Lifesciences, Medtronic, Potrero Medical, GE Healthcare, Philips North America, Caretaker Medical and Retia Medical. He is funded by an NIH/NCATS KL2 award for assessment of blood pressure and oxygenation in postoperative patients and a Wake Forest Hypertension and Vascular Research award for studying the relationship between serum renin and outcomes in patients with septic shock. AD consults for ALung Technologies . He is funded by NHLBI U grant for the PETAL network to study prevention and treatment of acute lung injury. The rest of the authors declare that they have no competing interest.

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**Availability of data and materials:** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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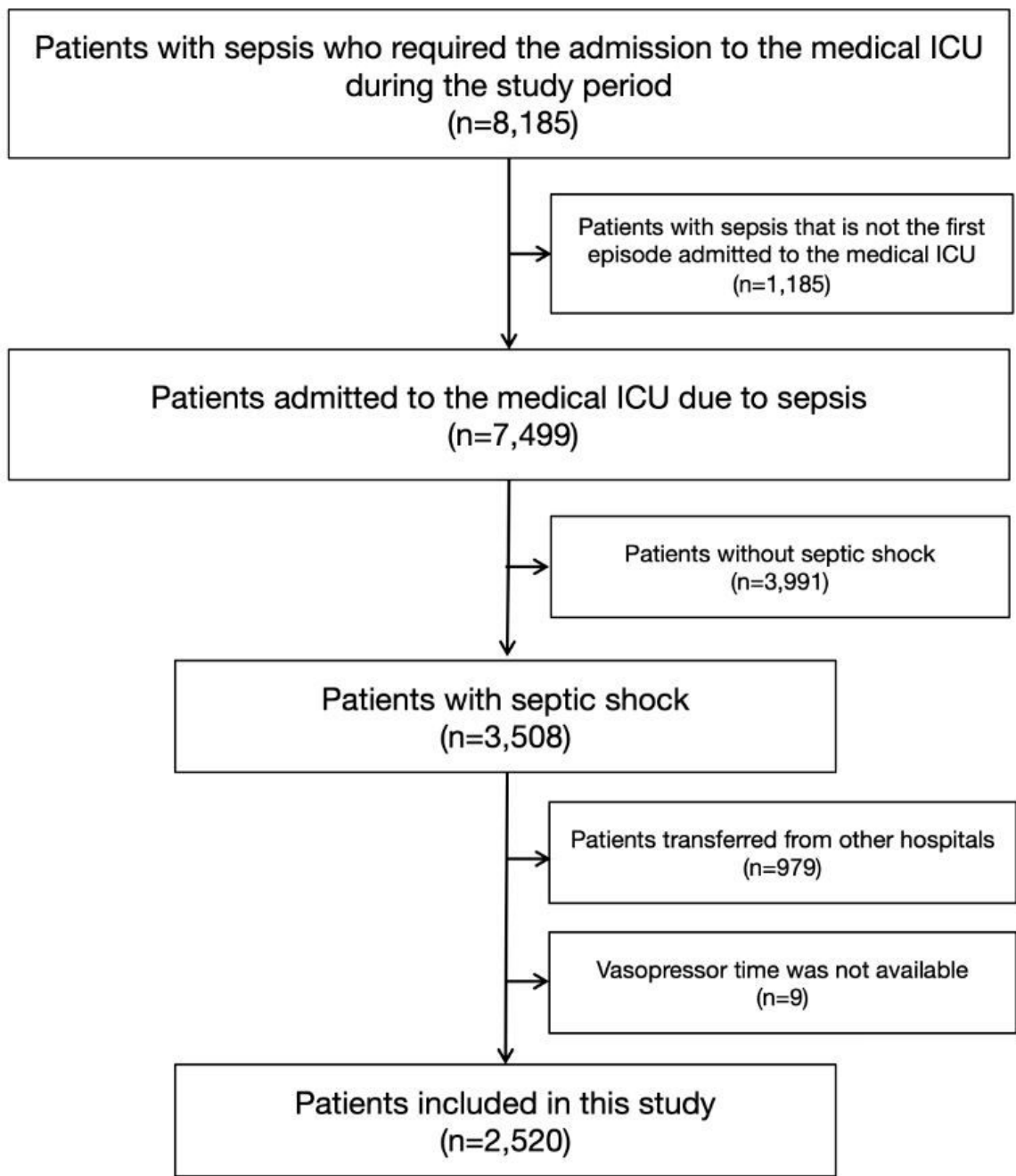
# Figures

**Figure 1.**



Figure 1

A total of 8,185 patients with sepsis based on Sepsis-II criteria were admitted to medical intensive care unit (ICU) between January 1, 2011 and December 31, 2020. We excluded patients requiring readmission to ICU with sepsis or septic during the study period (n = 686 patients), sepsis without septic shock (n = 3991 patients), admitted from other hospital (n = 979 patients) and patient where vasopressor initiation time cannot be accurately identified (n = 9 patients). Our final sample included 2520 patients.

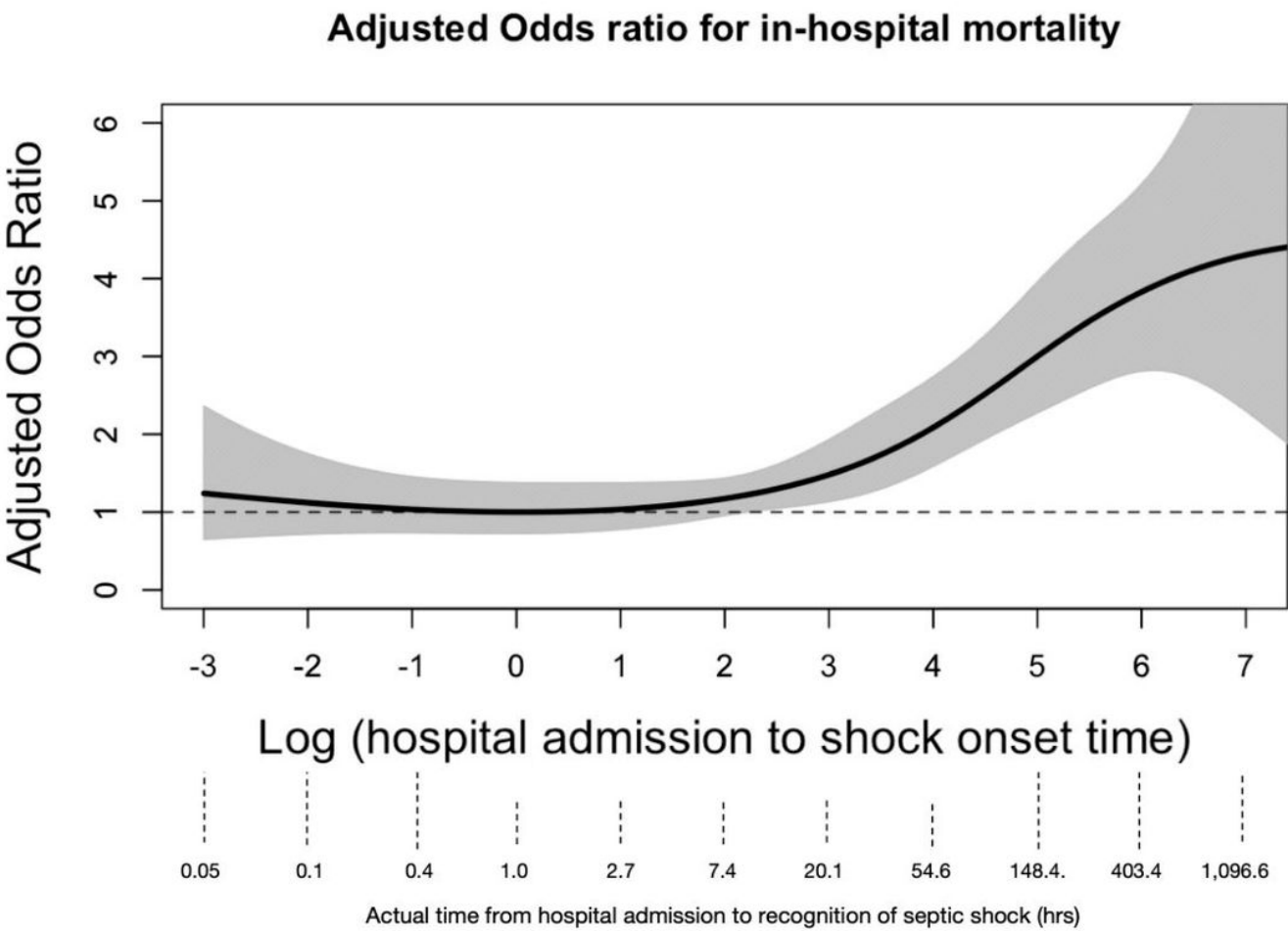## Adjusted Odds ratio for in-hospital mortality



## Figure 2

The odds ratio curve of the log-transformed admission-shock-onset-time for in-hospital mortality based on the additive logistic regression model. In this model, the baseline odds ratio was set at 1 hour of admission-shock-onset-time (zero in the log scale of the time). The odds ratio for in-hospital mortality continued to increase throughout the observation period.
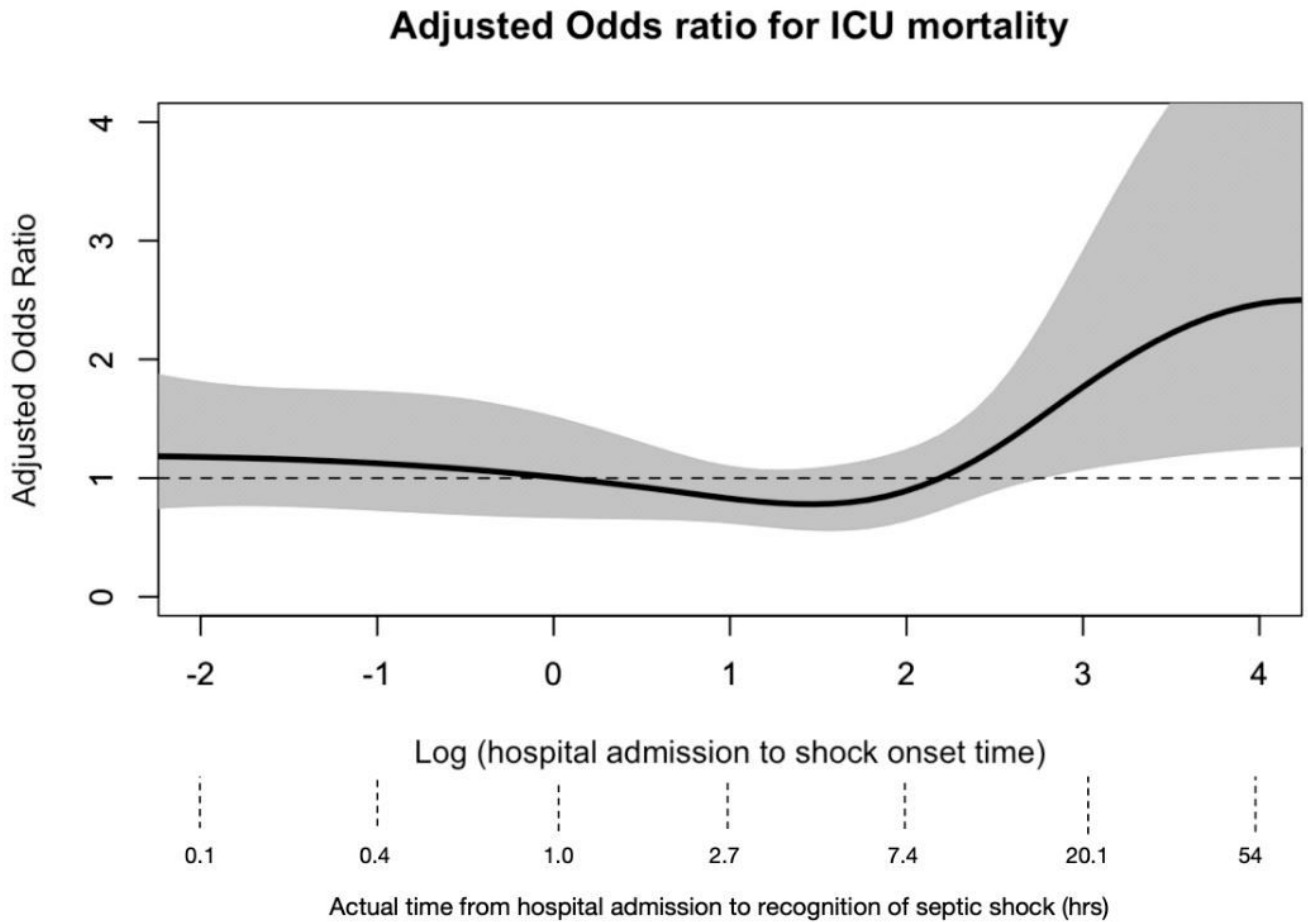
**Adjusted Odds ratio for ICU mortality**

Log (hospital admission to shock onset time)

Actual time from hospital admission to recognition of septic shock (hrs)

**Figure 3**

The odds ratio curve of the log-transformed admission-shock-onset-time for ICU mortality based on the additive logistic regression model. In this model, the baseline odds ratio was set at 1 hour of admission-shock-onset-time (zero in the log scale of the time). The odds ratio for in-hospital mortality continued to increase throughout the observation period.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile.docx