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Septic Shock Requiring Three Vasopressors: Patient Demographics and Outcomes

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OBJECTIVES: Septic shock is a common condition necessitating timely management including hemodynamic support with vasopressors. Despite the high prevalence and mortality, there is limited data characterizing patients who require three or more vasopressors. We sought to define the demographics, outcomes, and prognostic determinants associated with septic shock requiring three or more vasopressors.

DESIGN: This is a multicenter retrospective cohort of two ICU databases, Medical Information Mart for Intensive Care IV (MIMIC-IV) and electronic ICU-Clinical Research Database, which include over 400,000 patients admitted to 342 ICUs.

PATIENTS: Inclusion criteria entailed patients who were: 1) age 18 years old and older, 2) admitted to any ICU, 3) administered at least three vasopressors for at least 2 hours at any time during their ICU stay, and 4) identified to have sepsis based on the Sepsis-3 criteria.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 3447 patients met inclusion criteria. The median age was 67 years, 60.5% were male, and 96.6% had full code orders at the time of the third vasopressor initiation. Septic shock requiring three or more vasopressors was associated with 57.6% in-hospital mortality. Code status changes occurred in 23.9% of patients following initiation of a third vasopressor. Elevated lactate upon ICU admission (odds ratio [95% CI], 2.79 [2.73–2.85]), increased duration of time between ICU admission and third vasopressor initiation (1.78 [1.69–1.87]), increased serum creatinine (1.61 [1.59–1.62]), and age above 60 years (1.47 [1.41–1.54]) were independently associated with an increased risk of mortality based on analysis of the MIMIC-IV database. Non-White race and Richmond Agitation-Sedation Scale scores were not associated with mortality.

CONCLUSIONS: Septic shock requiring three vasopressors is associated with exceptionally high mortality. Knowledge of patients at highest risk of mortality in this population may inform management and expectations conveyed in shared decision-making.

KEYWORDS: sepsis; septic shock; vasopressors

Sepsis consists of a dysregulated immune response to infection leading to organ dysfunction. Septic shock comprises a subset of sepsis cases in which the host experiences vasodilatory hemodynamic collapse despite adequate volume resuscitation (1). Sepsis and septic shock are associated with an immense global burden of disease and comprise leading causes of ICU admission and death (2–8).

Management of septic shock entails a time-sensitive combination of fluids, antibiotics, and vasopressors (9). Norepinephrine and vasopressin are considered the first- and second-line vasopressor of choice, respectively, and robust evidence dictating

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KEY POINTS

Question: What are the demographics and outcomes for patients with septic shock who receive three or more vasopressors for at least 2 hours?

Findings: In this multicenter retrospective cohort study inclusive of 3447 patients, three vasopressor septic shock was associated with 57.6% in-hospital mortality. Nearly all patients had a full code order when the third vasopressor was initiated, and the duration of time between ICU admission and the third vasopressor initiation was associated with an increased risk of mortality.

Meaning: Understanding outcomes of septic shock requiring three vasopressors as well as specific risk factors for mortality may guide management and shared decision-making.

third line and subsequent pressor selection is limited (10–12). Administering additional pressors depends on several factors such as worsening hypotension or evidence of end-organ damage despite escalating doses of initial vasopressor. For example, the Surviving Sepsis Campaign advises early addition of vasopressin to norepinephrine (rather than escalating the dose of norepinephrine) when the blood pressure remains below goal (10). However, there are no universally accepted dosage thresholds to initiate a third vasopressor. Instead, vasopressor regimens are driven by consensus recommendations, medication availability, and clinical circumstances (10–12).

To our knowledge, a comprehensive assessment of septic shock patients requiring three or more vasopressors has not been performed. An improved understanding of this patient population may guide management strategies and inform prognostication. The aims of this study are to harness data from two large ICU databases to characterize patients with septic shock receiving three vasopressors, define outcomes, and identify features associated with mortality.

MATERIALS AND METHODS

Study Design and Data Sources

We conducted a multicenter retrospective analysis of two ICU databases containing comprehensive, deidentified data.

The first database, Medical Information Mart for Intensive Care IV (MIMIC-IV), is a publicly available dataset managed by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (13). MIMIC-IV provides data from seven ICUs within one hospital in the United States from 2008 to 2019.

The second, electronic ICU-Clinical Research Database (eICU-CRD), houses data from 335 ICUs across 208 hospitals in the United States from 2014 to 2015 (14). Because data from MIMIC-IV and eICU-CRD was previously de-identified, this analysis constituted National Institutes of Health exempt human subjects research, and no waiver of informed consent or institutional review board review was required (15).

Study Population

Inclusion criteria entailed individuals 18 years old and older identified as having sepsis who were admitted to any ICU and received three or more vasopressors for at least 2 hours.

Sepsis was defined according to the Sepsis-3 criteria as life-threatening organ dysfunction resulting from an abnormal host response to infection (1). Patients with sepsis were identified based on vital signs and laboratory abnormalities in addition to evidence of suspected infection (16). Patients who were admitted to the ICU with a primary diagnosis of sepsis and patients admitted for other indications who developed sepsis later in their admission were both included. In MIMIC-IV, suspected infection was defined based on antibiotic administration and microbiological culture sampling occurring within two days of one another. In eICU-CRD, suspected infection was defined based on antibiotic administration alone because microbiology culture data were unavailable.

The number and name of vasopressors administered were extracted from patient records (**e-Appendix 1**, outlines search terms, http://links.lww.com/CCX/B424).

Records were excluded when three vasopressor administration did not occur in an ICU, when three vasopressor administration occurred for fewer than 2 hours, when vasopressor administration did not occur via an IV route, or when certain variables (race, serum creatinine) were missing. If a patient had multiple ICU admissions featuring three vasopressor shock, data were gathered from the index ICU admission.

Data Extraction and Imputation

Data extracted from the two datasets included: patient demographics (e.g., age, sex, race), ICU admission characteristics (e.g., type of ICU, length of stay [LOS]), laboratory data (e.g., creatinine, lactate), IV fluid and medication administration, Sequential Organ Failure Assessment (SOFA) score, Charlson Comorbidity Index (CCI), and code status over time.

Sedating agents such as propofol can lower mean blood pressure and thus may necessitate vasopressor support independent from hypotension driven by sepsis pathophysiology (17). Sedative choice, dosing, and units varied significantly among patients in the databases' 209 hospitals, limiting comparisons. Richmond Agitation-Sedation Scale (RASS) scores were identified as a surrogate for sedation exposure that would offer a uniform comparator. RASS data were only available in MIMIC-IV and was extracted as a proxy for sedation exposure.

IV fluid administration was extracted during the 24 hours leading up to the initiation of the third vasopressor. **e-Appendix 2** (http://links.lww.com/CCX/B424) enumerates search terms used to identify IV fluids.

For data elements recorded serially during the ICU encounter such as laboratory values, SOFA scores, RASS scores, or code status, values obtained immediately before the initiation of the third vasopressor were selected. Patient age and body mass index were extracted at the time of ICU admission. For patients with multiple race identifiers, the race identity that occurred the most frequently in the patient's record was selected. If multiple code statuses were recorded with the same timestamp, the most restrictive code status was selected.

Code statuses were categorized ordinally from most to least restrictive as follows: comfort measures only, do not resuscitate (DNR) and do not intubate (DNI), DNR or DNI, or full code.

For patients with missing SOFA (n = 35 from eICU-CRD) and lactate (n = 24 from MIMIC-IV, n = 529 from eICU-CRD) data, imputation was used to avoid over-identification and distributional changes (18). Normal range data were substituted for missing data: SOFA of 0 and lactate of 1.

Risk Factor Identification and Model Development

A generalized additive model (GAM), a method with flexible capabilities for the combination of linear and nonlinear features, was used to characterize risk factors of mortality in this population (19). MIMIC-IV was used for initial model development and eICU-CRD was used for comparative analysis and to assess generalizability.

We selected variables for evaluation in the GAM model based on data available in eICU-CRD and MIMIC-IV as well as a literature review of known host-, infection-, and treatment-related variables associated with mortality in sepsis (**e-Appendix 3**, http://links.lww.com/CCX/B424) (20–27).

The final variables assessed in the GAM model were race, age, serum creatinine, lactate, SOFA score, the timing of the third vasopressor initiation relative to ICU admission, and RASS score. Because some race identities had limited representation, race was reconfigured in the model as a binary variable—non-White or White—to find the majority effect.

Outcomes and Statistical Analysis

The primary outcome was in-hospital mortality. Secondary outcomes included the prevalence of three vasopressor septic shock among patients with sepsis in the two databases, ICU and hospital LOS, code status transitions within 24 hours of third vasopressor initiation, and any subsequent code status transition following initiation of the third vasopressor and during the same hospitalization.

Continuous variables were described as mean values with SDs or medians with interquartile ranges after normality testing. The Kolmogorov-Smirnov and Shapiro-Wilk W tests were used to determine whether the underlying distributions of the variables were normal. Categorical values were described as event frequency and percentage (%). Differences in outcomes between the two databases were assessed by Student t test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and chi-square test for categorical (discrete) variables.

The associations between risk factors and mortality were presented as odds ratios (ORs) and 95% CIs. The ORs for categorical values were comparisons of two groups (e.g., White vs. non-White for race). The ORs for continuous values were described as figures to identify trends by range and tabulated for risk comparisons based on values from the literature or, when literature was not available, averages from datasets.

Sensitivity analyses (**e-Tables 1–3**, http://links.lww.com/CCX/B424) were performed to confirm if the following issues had a significant effect on the model's results: 1) the presence or absence of RASS; 2) the inclusion or exclusion of RASS in the model; and 3) multiple records of race.

All data curation was performed with Google BigQuery (Google, Mountain View, CA; Version 1.21.0). Data cleaning and statistical analysis were performed using SciPy (SciPy Developers, Online Open Source Community; Version 1.2.2) and Python (Python Software Foundation, Wilmington, DE; Version 3.7) with ORs calculated using R (R Foundation for Statistical Computing, Vienna, Austria; Version 4.2) (28).

RESULTS

Patient Characteristics

Of the 315,460 patients in the MIMIC-IV database, 1,347 patients (0.4%) met the inclusion criteria. Of the 139,367 patients in the eICU-CRD database, 2,100 patients (1.5%) met the inclusion criteria. Combing the two databases yielded a total sample of 3447 (0.76%) patients with septic shock requiring three vasopressors for at least 2 hours (**Fig. 1**).

Baseline patient characteristics are shown in **Table 1**. There were several significant differences between patients in the two databases. Patients from MIMIC-IV identified less often as White and more often as male. The MIMIC-IV cohort was overall sicker based

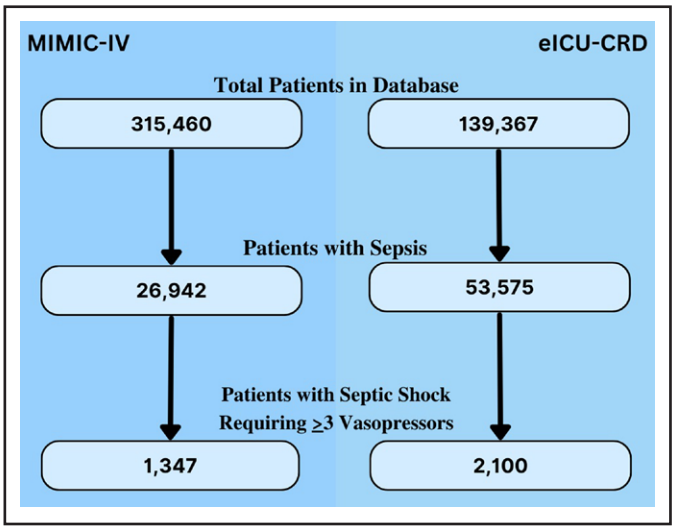

Figure 1. Patients with sepsis and septic shock requiring three vasopressors within each database. eICU-CRD = electronic ICU-Clinical Research Database, MIMIC-IV = Medical Information Mart for Intensive Care IV.

indicators such as CCI, SOFA score, and creatinine and more likely to have a full code status. Patients in the MIMIC-IV database also received significantly more IV fluid administration leading up to initiation of the third vasopressor.

Outcomes

Patient outcomes are shown in **Table 2**. The overall in-hospital mortality rate was 57.6%. Among all patients with sepsis in the two databases (n = 80,517), the prevalence of septic shock requiring three vasopressors was 4.3%. The overall median ICU LOS and median hospital LOS were 4.1 and 9.0 days, respectively. Mortality, prevalence of three vasopressor septic shock, ICU LOS, and hospital LOS were all significantly higher in the MIMIC-IV cohort compared to eICU-CRD.

Regarding code status, 11.8% patients transitioned to a more restrictive code status within 24 hours of being initiated on a third vasopressor, and 23.9% transitioned at any point after initiation of the third vasopressor (**e-Tables 4** and **5**, http://links.lww.com/CCX/B424). Shifts in code status occurred less frequently in the MIMIC-IV cohort (**e-Tables 6–9**, http://links.lww.com/CCX/B424).

Prognostic Indicators

The GAM model identified several variables that were associated with an increased probability of mortality in the MIMIC-IV cohort, including age above 60 years at ICU admission, elevated creatinine and lactate levels immediately before the initiation of the third vasopressor, and increased duration of time between ICU admission and third vasopressor initiation (**Table 3**). Analysis of the eICU-RD database yielded similar results, although SOFA score was associated with an increased risk of mortality in eICU-CRD but not MIMIC-IV.

Each significant variable had a dynamic association with mortality (**e-Figs. 1** and **2**, http://links.lww.com/CCX/B424). Increases in age after age 60 were associated with an exponential rise in the risk of mortality while increasing lactate values, SOFA score, and time delay between ICU admission and third vasopressor initiation had a positive correlation with risk of mortality that followed a linear pattern. The association between serum creatinine and mortality was more complex and resembled a bimodal distribution with peak relative

TABLE 1.
Septic Shock Patient Demographics and Comparison Between Medical Information Mart for Intensive Care IV and Electronic ICU-Clinical Research Database

Variable	Medical Information Mart for Intensive Care IV ($n = 1347$)	Electronic ICU-Clinical Research Database ($n = 2100$)	Comparison p	Overall ($n = 3447$)
Age (yr), median (Q1–Q3)	67.0 (56.0–76.0)	66.0 (56.0–75.0)	0.440	67.0 (56.0–75.0)
Body mass index, median (Q1–Q3)	28.2 (24.3–32.9)	28.5 (24.2–34.2)	0.107	28.3 (24.3–33.8)
Race, White, *n* (%)[a]	796 (59.1)	1579 (75.2)	< 0.001	2375 (68.9)
Sex, male, *n* (%)	863 (64.1)	1221 (58.1)	< 0.001	2084 (60.5)
Charlson Comorbidity Index, median (Q1–Q3)	6.0 (5.0–8.0)	4.0 (2.0–6.0)	< 0.001	5.0 (3.0–7.0)
Sequential Organ Failure Assessment score, median (Q1–Q3)	10.0 (7.0–12.0)	8.0 (5.0–12.0)	< 0.001	9.0 (6.0–12.0)
Richmond Agitation-Sedation Scale score, median (Q1–Q3)[b]	−4.0 (−5.0 to −2.0)	NA	NA	
Creatinine (mmol/L), median (Q1–Q3)	1.8 (1.1–2.8)	1.6 (1.0–2.6)	< 0.001	1.7 (1.1–2.7)
Lactate (mmol/L), median (Q1–Q3)	4.4 (2.7–8.1)	4.4 (2.1–8.9)	0.027	4.4 (2.4–8.5)
Fluid administration (mL), mean (SD)[c]	1090.0 (1981.7)	198.5 (684.5)	< 0.001	486.1 (1384.1)
Time from ICU admission to third vasopressor initiation (hr), median (Q1–Q3)	16 (6.0–55.0)	10.8 (2.3–39.5)	< 0.001	12.4 (4.0–45.0)
Code status, *n* (%)[d]				
Full code	1310 (97.3)	2021 (96.2)	< 0.001	3331 (96.6)
DNR	28 (2.1)	59 (2.8)		87 (2.5)
DNI	0 (0)	9 (0.4)		9 (0.3)
DNR and DNI	8 (0.6)	9 (0.4)		17 (0.5)
Comfort measures only	1 (0.1)	2 (0.1)		3 (0.1)
Type of ICU, *n* (%)[d]				
Cardiac	455 (33.8)	762 (36.3)	0.200	1217 (35.3)
Medical	631 (46.8)	1170 (55.7)		1801 (52.2)
Neuro	38 (2.8)	67 (3.2)		105 (3.0)
Surgical	223 (16.6)	101 (4.8)		324 (9.4)

DNI = do not intubate, DNR = do not resuscitate, NA = not applicable.

[a]Eighteen patients were identified as having multiple races. See e-Tables 1 and 2 (http://links.lww.com/CCX/B424) for additional detail.

[b]Richmond Agitation-Sedation Scale was not available in the electronic ICU database.

[c]Despite the non-normal distribution, the mean and SD, rather than median, is presented to facilitate clinical interpretation.

[d]For code status and type of ICU, the distributions of outcomes were compared between the two databases, yielding one *p* value.

mortality risk at values of 4 and 13. The median time from ICU admission to third vasopressor initiation was significantly lower for patients who survived to discharge compared with those with in-hospital mortality (27.3 hr [2.6–28.6 hr] vs. 43.0 hr [5.0–57.8 hr]).

The other variables of the GAM model—race identity and RASS score—were not associated with significantly higher odds of mortality in either database. When data for individual race identifiers was compared, there were a higher percentage of Black patients with sepsis initiated on a third vasopressor as compared with White patients with sepsis (5.0% vs. 3.6%; $p < 0.0001$). In the dichotomized race comparison, in-hospital mortality was not significantly different between non-White and White patients (61.8% vs. 55.5%; $p = 0.235$).

TABLE 2.
Septic Shock Outcomes

Variable	Medical Information Mart for Intensive Care IV ($n = 1347$)	Electronic ICU-Clinical Research Database ($n = 2100$)	Comparison p	Overall ($n = 3447$)
ICU length of stay (d), median (Q1–Q3)	5.6 (2.0–13.6)	3.5 (1.4–8.0)	< 0.001	4.1 (1.7–10.1)
In-hospital length of stay (d), median (Q1–Q3)	11.0 (3.0–23.0)	8.3 (3.2–16.2)	< 0.001	9.0 (3.0–18.6)
In-hospital mortality, *n* (%)	860 (63.8)	1124 (53.5)	< 0.001	1984 (57.6)

TABLE 3.
Generalized Additive Model Variables With Associated Odds Ratio for Mortality for Medical Information Mart for Intensive Care IV and Electronic ICU-Clinical Research Database

	Medical Information Mart for Intensive Care IV ($n = 1347$)	Electronic ICU-Clinical Research Database ($n = 2100$)
Variable	OR (95% CI)	OR (95% CI)
Race (White)	0.79 (0.77–0.82)	1.03 (0.99–1.06)
Age (yr)	1.47 (1.41–1.54)	1.56 (1.50–1.62)
Creatinine (mmol/L)	1.61 (1.59–1.62)	1.69 (1.65–1.74)
Lactate (mmol/L)	2.79 (2.73–2.85)	3.23 (2.87–3.63)
Sequential Organ Failure Assessment	1.19 (0.86–1.65)	3.84 (3.47–4.26)
Third vasopressor initiation time from ICU admission (hr)	1.78 (1.69–1.87)	2.16 (2.02–2.31)

OR = odds ratio.

Statistical significance was assessed based on comparison to a priori established reference points drawn from the literature or, when literature was not available, medians from the analytic sample: age 60, creatinine 1.2, lactate 2.0, Sequential Organ Failure Assessment score 0, and third vasopressor initiation 12.4 hr (median from the analytic sample) (29, 30).

DISCUSSION

This multicenter retrospective analysis of 3447 patients found that septic shock requiring three vasopressors for at least 2 hours occurred infrequently but was associated with significant mortality. Nearly all patients who received a third vasopressor had a full code status when the third vasopressor was initiated, and most of these patients remained full code through the end of their ICU stay. Multiple features associated with mortality were identified including a longer interval from ICU admission to initiation of the third vasopressor.

We speculate that septic shock necessitating three or more vasopressors that occurs later in a patient's ICU course may have distinct features and etiologies that confer higher mortality. Prior literature indicates that hospital acquired sepsis, as compared with community acquired sepsis, is associated with a sources, pathogens, and outcomes including worsened outcomes including mortality (31). The timing of triple vasopressor septic shock may therefore inform specific management considerations and prognostication.

The mortality associated with septic shock requiring three or more vasopressors is exceptionally high, resting at the upper estimate of mortality from previous studies including those evaluating severe septic shock (2, 3, 23, 32–34). Combined with the high percentage of patients who remained full code, our study suggests that this patient population may be subject to invasive end-of-life interventions. Prior data indicates that sepsis is associated with worse outcomes for patients who experience in-hospital cardiac arrest

(29). To set appropriate expectations as part of shared decision-making, we suggest that initiation of a third vasopressor prompt goals of care discussions. The prognostic indicators of mortality identified in our study offer additional insight into which patients are most at risk of death.

Mortality risk correlated with several factors including age, serum creatinine, and serum lactate. These findings are consistent with prior literature (30, 35). The large CIs at the extreme ends can be attributed to the small number of patients with those high values. Although the overall concave curve of creatinine is consistent with the patterns seen in previous studies, the bimodal appearance of the serum creatinine curve has several possible explanations including outliers and patients receiving renal replacement therapy. The lack of data before ICU admission including baseline serum creatinine values made it difficult to distinguish between the presence of acute kidney injury and/or chronic kidney disease, which may confound the relationship between serum creatinine and mortality.

Prior analyses have found racial disparities in sepsis including increased frequency, hospitalization rate, organ dysfunction, complications, and mortality in non-White patients (36–39). In our study, there was not a statistically significant difference in mortality from three vasopressor shock across self-reported race-ethnicity, although our approach to treating race in a binary manner may have limited opportunities for demonstrating differences.

Strengths and Limitations

The strengths of this study include a large sample of patients from over 200 hospitals and over 300 ICUs and findings that are consistent with prior studies of septic shock. Additionally, the current study focuses on a patient population that had not been previously investigated in detail and with sufficient statistical power.

There are several important limitations to this study. First, the retrospective nature precludes establishing causal relationships and fully understanding the rationale for when and why a third vasopressor was initiated.

Second, there are multiple features of the databases that the limit interpretation of the results: patient data, ranging from 2008 to 2019, may not reflect the most recent practices; the eICU-CRD database does not contain microbiology data including cultures such that suspected infection aspect of sepsis definition was limited to antibiotic administration alone; and the timing, amount, and impact of sedation, IV fluid, and other medication administration could not be fully determined.

The MIMIC-IV and eICU-CRD databases do not contain data before ICU admission apart from comorbid conditions, and only MIMIC-IV contains RASS scores. Confirming antibiotic regimens, timing of antibiotic administration, and the possibility of sedation-related hypotension was therefore not possible based on available data. Similarly, most patients (59% of MIMIC-IV, 87% of eICU-CRD) did not have IV fluid data available during the 24 hours before third vasopressor initiation; the limited data available was included in our analysis given the significant role fluid resuscitation plays is management of sepsis. With these challenges, it is also difficult to determine to what extent other etiologies of hypotension such as hypovolemia, sedation-induced vasoplegia, and cardiogenic phenomena were present in addition to the septic process.

Additionally, there were significant differences in the MIMIC-IV and the eICU-CRD cohorts including one different prognostic indicator. Assessing multiple databases, however, provided statistical power and allowed for modeling of heterogeneity of treatment effect. Sensitivity analyses, including those assessing the impact of missing data, support internal validity of our findings despite significant differences in the two databases.

Third, specifying a 2-hour minimum duration of three vasopressor therapy excluded some patients, particularly those who expired abruptly after initiation of a third vasopressor. We imposed this cutoff to identify patients in sustained septic shock whose vasopressor requirement was attributable to sepsis pathophysiology rather than transient phenomena such as loss of peripheral vascular tone during intubation.

Finally, our GAM model assessed six variables, but other predictors of in-hospital mortality may exist in this population. These six variables were selected based on previously published predictors of mortality in sepsis and the data that was available in both datasets. Two of these variables, serum lactate measurements and SOFA scores, were missing in some patients and required imputation, which may have introduced selection bias. To address this, we imputed missing values with a default

or normal value. While this approach aligns with clinical practices and reduces the risk of overestimating illness severity, it may introduce bias by not fully accounting for the uncertainty of missing data. Although more complex methods were considered, we chose simple imputation as it best reflects the clinical context where missing values often indicate normal conditions.

Future Directions

Comparing septic shock outcomes based on which vasopressor is selected as the third vasopressor may inform management of this critically ill patient population, as would assessing if timing of the third vasopressor initiation relative to the initial two vasopressors (e.g., at lower or higher doses of the initial two pressors) influences outcomes. Additionally, similar analyses should be carried out for patients requiring three or more vasopressors for indications other than septic shock, as pathophysiology varies considerably across conditions.

CONCLUSIONS

In this multicenter retrospective cohort, septic shock necessitating three or more vasopressors for at least 2 hours carried an exceptionally high mortality burden at the upper limit of prior mortality estimates. Code status changes occurred infrequently after initiation of the third vasopressor. Prognostic indicators, including the time interval from ICU admission to third vasopressor initiation, can inform goals of care discussions for this population.

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Dr. Kistler takes responsibility for the integrity of the data, the accuracy of the data analysis, and the content of the article including and especially any adverse effects. All authors took part in study design. Dr. Kwak, Dr. Madushani, Dr. Adhikari, Ms. Yan, Ms. Sebbane, Ms. Yanes, and Mr. Restrepo conducted search queries and performed data analysis. All authors had access to all data and contributed substantially to data interpretation. Drs. Kwak and Kistler drafted the article, and all authors then contributed substantially to its revision. Drs. Rosenthal, Wong, and Celi provided mentorship throughout the conduct of this work. All authors approve of the article for publication.

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The URL of the data sources, search queries, and Jupyter Notebooks containing the scripts used to extract data and generate descriptive statistics included in this article are available at: https://github.com/MIT-LCP/three-pressor-problem.

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