Time to Vasopressor Initiation Is Not Associated With Increased Mortality in Patients With Septic Shock

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Study objective: The optimal timing of vasopressor initiation in septic shock remains unclear. Our objective was to evaluate the association between time to vasopressor initiation and mortality.

Methods: This was a retrospective cohort study of patients with septic shock in the OneFlorida Data Trust, a statewide repository of health care data. We included patients if they received vasopressors during hospitalization after at least 1 episode of hypotension (systolic blood pressure ≤100 mmHg) and had either (1) an International Classification of Disease 9 or 10 code for sepsis, or (2) an International Classification of Disease code for infection and received IV antibiotics. The primary outcome was 90-day mortality. The secondary outcome was vasopressor-free days. We used multiple logistic regression with Least Absolute Shrinkage and Selection Operator for variable selection to assess associations with 90-day mortality.

Results: There were 4,699 patients with septic shock between 2012 and 2018 included. The primary outcome, 90-day mortality, was present in 34% (n=1,610). Time to vasopressor initiation was not found to be associated with 90-day mortality (odds ratio [OR] 1.01; 95% confidence interval [CI] 1.00 to 1.02). Independent predictors included age (OR 1.04; 95% CI 1.04 to 1.05), mechanical ventilation (OR 2.98; 95% CI 2.56 to 3.48), laboratory components of the Sequential Organ Failure Assessment score (OR 1.18; 95% CI 1.14 to 1.23), lactate level (OR 1.10; 95% CI 1.08 to 1.13), chronic hypertension (OR 0.60; 95% CI 0.52 to 0.70), and liver disease (OR 1.54; 95% CI 1.30 to 1.82). Time to vasopressor initiation was not found to be an independent predictor of vasopressor-free days.

Conclusion: Time from first hypotensive episode to vasopressor initiation was not found to be associated with 90-day mortality or vasopressor-free days in this large cohort of septic shock patients. [Ann Emerg Med. 2025;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

An estimated 40% to 50% of patients with septic shock will die.[1] Vasopressors are a mainstay of septic shock management, but the optimal timing of vasopressor initiation remains controversial. Consensus guidelines recommend a progressive approach to the management of sepsis-induced hypotension, starting with an initial intravenous fluid bolus, followed by vasopressor initiation for hypotension refractory to intravenous fluid administration targeting a mean arterial pressure of 65 mmHg.[2,3] However, there remains a lack of consensus in the current literature regarding when vasopressors should be initiated. Although hypotension is clearly associated with harm, whether earlier time to vasopressor mitigation can mitigate that remains unclear.[4-7]

Importance

Vasopressor administration is central to septic shock management to maintain critical organ perfusion.[2,8] However, recent studies are conflicting, with some suggesting harm associated with very early vasopressor initiation[9-12] prior to optimization of fluid status, whereas others suggest adverse outcomes associated with delays in

Editor's Capsule Summary

What is already known on this topic

The optimal timing of vasopressor administration in septic shock is uncertain.

What question this study addressed

Is time from hypotension identification to vasopressor administration associated with mortality in septic shock?

What this study adds to our knowledge

In this observational cohort study of 4,699 patients, the time between first hypotension and vasopressor initiation was not associated with mortality and was not an independent predictor of vasopressor-free days.

How this is relevant to clinical practice

A personalized approach using individual characteristics may be appropriate for clinicians applying vasopressor therapy when treating people with sepsis-induced hypotension.

vasopressor initiation.[13-16] Although there may be a physiologic rationale that favors earlier vasopressor administration, this benefit has not been convincingly shown in the published literature. Several larger studies of vasopressor timing include data from septic shock patients in the late 1990s and early 2000s,[10,17] which may no longer be relevant given recent advances in septic shock management. Although not designed to explicitly study time to vasopressor initiation, a much-anticipated clinical trial comparing progressive fluid resuscitation versus early vasopressor initiation in sepsis also did not find any differences in mortality.[18]

Given the lack of recent, large studies of vasopressor timing in septic shock, we sought to evaluate the association between timing of vasopressor initiation and relevant clinical outcomes. We previously found that prolonged time to vasopressor initiation was associated with increased organ failure when vasopressor initiation was delayed more than 20 hours, but we did not find shorter delays to predict worsening organ failure.[19]

Goals of the Investigation

Our objective was to assess the association between time to vasopressor initiation from first hypotensive episode and 90-day mortality in this large, more recent, retrospective cohort of septic shock patients. We also sought to evaluate the association between timing of vasopressor initiation and the secondary outcome, vasopressor-free days.

METHODS

Study Design and Data Source

Our study was a retrospective cohort analysis of data from the OneFlorida Data Trust. The OneFlorida Database is a large, statewide repository of health care data curated by the OneFlorida Clinical Research Consortium, a clinical research network of partnered academic institutions and health systems throughout the state of Florida.[20-22] The OneFlorida Data Trust includes diagnoses, procedures, medications, demographics, and other data elements reported in the Patient-Centered Outcomes Research Institute Common Data Model, as well as electronic health record data.[21-25] The OneFlorida Clinical Research Consortium is part of the National Patient-Centered Clinical Research Network (PCORnet), which includes standardized, regular data quality checks and harmonization across all sites in the PCORnet system.[24,26] We previously used the OneFlorida Data Trust for septic shock research and have described our methods for data abstraction and variable transformation.[27]

We considered eligible encounters from January 2012 to July 2018 for inclusion in our analytic cohort. We selected this time period to reflect recent management of septic shock. Our methods follow STROBE guidelines for reporting (see Supplementary Material, available at http://www.annemergmed.com). Our study was approved by the University of Florida International Review Board (IRB #201802013).

Data Collection and Abstraction of the Septic Shock Cohort

We identified septic shock encounters using the following criteria: patients receiving vasopressors after at least one episode of documented hypotension (systolic blood pressure [SBP] $\leq$ 100 mmHg) during their hospital encounter and either (1) having an explicit International Classification of Disease (ICD) 9 or 10 code for sepsis during their hospital encounter, or (2) having an ICD code for infection and along with receiving intravenous antibiotics during the encounter (see Tables E1 to E4, available at http://www.annemergmed.com, for sepsis and infection codes and included intravenous antibiotics). We have previously published our rationale for this approach.[27] Briefly, we considered presumed infection as a documented infection code with intravenous antibiotic administration, and documented hypotension along with

vasopressor administration to represent organ dysfunction.[27] These modifications are similar to other previously described adaptations.[28,29] We chose SBP $\leq$ 100 mmHg consistent with other emergency department literature[4,5,30] and Surviving Sepsis Campaign consensus statements.[1,8] We a priori decided to focus on patients who received vasopressors within the first 24 hours after presentation and excluded patients who received vasopressors more than 24 hours after triage. We chose this strategy to focus on early septic shock management and not hospital-acquired sepsis or septic shock. We excluded patients who were missing SBP measurements, race and ethnicity information, as well as deceased patients missing a corresponding date of death. Patients were also excluded if they were recorded as receiving vasopressors prior to triage due to an incalculable time to vasopressor initiation. Additionally, patients were excluded if they received vasopressors without any documented hypotension or received vasopressors before documented hypotension. For patients with more than one encounter, we used data from the first encounter (see flow diagram, Figure E1, available at http://www.annemergmed.com).

Prior to exclusion criteria, there were 18,197 encounters corresponding to 15,654 unique patients in the OneFlorida Data Trust who received vasopressors and had an explicit diagnosis of sepsis and/or an infection code and received intravenous antibiotics between January 2012 and July 2018.

Demographic, Comorbidity, and Disease Severity Variables and Data Processing

We collected demographic data, including age, biologic sex, race and ethnicity, and insurance status. We used ICD-9 and 10 codes to abstract data for comorbidities including liver disease, hypertension, chronic obstructive pulmonary disease, end-stage renal disease, HIV, and congestive heart failure (see Table E5, available at http://www.annemergmed.com).

To account for disease severity, we quantified organ failure using the laboratory components of the Sequential Organ Failure Assessment (SOFA) score, or labSOFA, as previously described.[27] Briefly, labSOFA is a combination of the values for the renal, hepatic, and hematologic components of the SOFA score. We imputed the median value for the SOFA score component for patients with missing bilirubin, platelet, or creatinine values. We used mechanical ventilation dependence to account for respiratory dysfunction. To further account for illness severity, we abstracted initial lactate values, defined as the first lactate measurement available during the patient encounter. We imputed values for the 267 patients (6% of patient cohort) missing lactate measurements using the random forest algorithm MissForest with 6 iterations[31] and used the imputed version of the lactate variable in multivariable regression modeling.

Time to Vasopressor Initiation and Treatment Variables

For time-related variables, we used the triage time for the beginning of the patient encounter. We defined triage as the date and time of the first documented vital signs. Study definitions are included in Box 1.[1,8,32,33] We measured time to vasopressor initiation from first hypotensive episode as opposed to time from triage as patients may not have been hypotensive at the time of triage. We investigated the association between time to vasopressor initiation and the primary outcome, 90-day mortality, as a continuous variable from 0 to 24 hours. We calculated intravenous fluid volume as the volume of intravenous fluids given in the first 6 and 12 hours after triage. Further definitions are included in Box 1.

Study Outcomes

The primary outcome was 90-day mortality. Secondary outcomes were inhospital death, defined as death during the hospital encounter, and vasopressor-free days. We used drug

Box 1. Study definitions.

Term	Definition
Triage time	Date and time of first record vital signs
Hypotension	Systolic blood pressure (SBP) less than or equal to 100 mmHg, consistent with guidelines[1,8]
Time to vasopressor initiation	Time of vasopressor administration from first hypotensive blood pressure measurement (SBP $\leq$ 100 mmHg) after triage
Vasopressors	Medications that increase blood pressure (norepinephrine, vasopressin, phenylephrine, epinephrine, dobutamine, dopamine)
Intravenous fluids	Lactated ringers, normal saline solution (0.9% NS), plasmalyte
labSOFA	laboratory components of the Sequential Organ Failure Assessment score (creatinine, bilirubin, platelet count)
Vasopressor-free days	Days alive and without vasopressor use within 28 days after the first documented hypotensive episode[32,33]

order and end dates to determine vasopressor use. Patients who died within the first 28 days were assigned zero vasopressor-free days, consistent with what others have described.[32,33]

Statistical Analyses

We calculated counts and proportions for categoric variables, means and SDs for normally distributed continuous variables, and medians and interquartile ranges (IQRs) for all other continuous variables. We analyzed the relationships between 90-day mortality and categoric covariates using chi-squared tests and the relationships between 90-day mortality and continuous covariates using Wilcoxon rank-sum tests.

Multivariable Models

We used multiple logistic regression to analyze significant predictors of 90-day mortality in our cohort of patients with septic shock. We used the Least Absolute Shrinkage and Selection Operator, or LASSO, method for variable selection for the multivariable model (alpha = 1, nfolds = 10). The LASSO method is a penalized regression method used for variable selection and regularization. It considers all of the candidate variables and reduces the coefficients of some variables to zero, thus eliminating them from the final model. The LASSO method reduces overfitting and bias in variable selection and thus is appropriate for this size and type of data.

Candidate predictors for the model are listed in Table E6 (available at http://www.annemergmed.com). We selected candidate variables using domain knowledge and, as per our a priori plan, used LASSO for variable selection. As LASSO has limitations with highly colinear variables, all eliminated variables were subsequently reviewed and assessed to ensure their omission was appropriate. We used variance inflation factors to check for multicollinearity, all of which were less than 2. We a priori planned to investigate the relationship between vasopressor timing and mortality as a linear variable and, as a secondary analysis, in 2-hour intervals from documented hypotension. We also investigated time to vasopressor initiation in 2-hour intervals from documented hypotension in order to assess for nonlinear relationships or indications of varying responses, such as hypothetical harm with premature vasopressor initiation before adequate fluid resuscitation, as well as harm with very delayed administration, and a more ideal intermediate time. We used R Studio (Vienna, Austria) version 12 for statistical analyses.[34]

RESULTS

Characteristics of the Study Subjects

There were 4,699 unique patients with septic shock in the final analytic cohort, after exclusions (see flow diagram, Figure E1). The median age was 62 years [IQR 52 to 72 years]. The most common comorbid conditions were hypertension (66%), congestive heart failure (31%), and liver disease (22%). Furthermore, demographic data and comorbid conditions are included in Table 1. Almost two-thirds of the patients required mechanical ventilation (64%). The median initial lactate was 2.5 mmol/L [IQR 1.5 to 4.5]. The observed 90-day mortality was 34% (n=1,610), whereas inhospital mortality was 26% (n=1,239).

Regarding clinical management, the median time to antibiotic administration from triage was 105 minutes [IQR 36 to 297] and the median volume of intravenous fluids administered at 6 and 12 hours were 500 mL [IQR 0 to 2,000] and 1,000 mL [IQR 0 to 2,000] respectively. The most common vasopressor administered was norepinephrine (n=3,557; 76%). The frequency of other vasopressors used is included in Table E7 (available at http://www.annemergmed.com). The median time to vasopressor initiation from first hypotensive episode was 2.68 hours [IQR 0.72 to 6.92]. Median vasopressor-free days were 23 days after first hypotensive episode, with a wide IQR [6 to 26]. Additional illness severity, management, and outcomes data are included in Table 1. Relationships between 90-day mortality and demographic data, clinical variables, and outcomes are included in Table 2.

Regression Models

In the LASSO logistic regression model for 90-day mortality, time to vasopressors initiation was not found to be associated with 90-day mortality (odds ratio [OR] 1.01; 95% CI 1.00 to 1.02). Independent predictors of 90-day mortality included age (OR 1.04; 95% CI 1.04 to 1.05), mechanical ventilation use (OR 2.98; 95% CI 2.56 to 3.48), labSOFA (OR 1.18; 95% CI 1.14 to 1.23), lactate (OR 1.10; 95% CI 1.08 to 1.13), hypertension (OR 0.60; 95% CI 0.52 to 0.70), and liver disease (OR 1.54; 95% CI 1.30 to 1.82). Our model also controlled for variables retained by LASSO but not found to be significantly associated with the primary outcome, including time to antibiotics, intravenous fluid volume within the first 6 hours, congestive heart failure, chronic obstructive pulmonary disease, and HIV infection status are included in Table 3. Figure A shows the relationship between time to vasopressor initiation as a linear variable and the predicted probability of 90-day mortality, with time to

Table 1. Demographic data, illness severity, and management.

Characteristics	Overall (n=4,699) % (n) or Median [IQR]
Age, y	62.3 [52.2, 72.3]
Sex	
Male	54.7% (2,572)
Female	45.3% (2,127)
Race	
Black	27.0% (1,270)
Hispanic	1.9% (89)
Other	2.0% (93)
White	69.1% (3,247)
Payer type (insurance)	
Medicare	16.0% (754)
Medicaid	18.8% (882)
Private	12.6% (592)
Medicare + private	39.4% (1,851)
Missing	3.7% (176)
Other	5.4% (256)
Uninsured/charity	4.0% (188)
Liver disease	
Yes	22.4% (1,053)
No	77.6% (3,646)
CHF	
Yes	31.3% (1,472)
No	68.7% (3,227)
Hypertension	
Yes	66.0% (3,102)
No	34.0% (1,597)
COPD	
Yes	18.5% (869)
No	81.5% (3,830)
ESRD	
Yes	8.3% (391)
No	91.7% (4,308)
HIV	
Yes	2.5% (117)
No	97.5% (4,582)
Mechanical ventilation	
Yes	63.8% (2,998)
No	36.2% (1,701)
Initial lactate value*, mmol/L	2.5 [1.5, 4.5]
LabSOFA score	
Total LabSOFA	2.0 [1.0, 4.0]
Renal SOFA	1.0 [0.0, 2.0]
Hepatic SOFA	0.0 [0.0, 0.0]
Coagulation SOFA	0.0 [0.0, 1.0]
Time to antibiotics†, min	105.0 [36.0, 297.0]
Ninety-day mortality	
Death	34.3% (1,610)
Survival	65.7% (3,089)
Inhospital death	
Death	26.4% (1,239)
Survival	73.6% (3,460)
First 6-hour intravenous fluid resuscitation‡, mm	500 [0, 2,000]
First 12-hour intravenous fluid resuscitation‡, mm	1,000 [0, 2,000]
Vasopressor-free days$, d	23 [0, 26]

*Based on patients with nonmissing data (267 missing and subsequently imputed lactate values not included).
†Winsorized.
‡After time of triage.
$Vasopressor-free days defined as days free of vasopressor use during first 28 days after first documented vasopressor initiated.

vasopressor initiation as an unadjusted variable. Figure B illustrates the relationship between time to vasopressor initiation and the predicted probability of 90-day mortality, while adjusting for other variables retained in the model using marginal effects plots.[35]

Time to vasopressor initiation was not found to be associated with 90-day mortality when evaluated in 2-hour intervals from time from hypotension, rather than as a linear variable. There was no significant association between any 2-hour interval of time from hypotension to vasopressor administration and 90-day mortality, while adjusting for other variables in the model (Table E8, available at http://www.annemergmed.com).

Time to vasopressor initiation was not found to be associated with vasopressor-free days (coefficient –0.04, SE 0.03) in the linear regression model for vasopressor-free days, using LASSO for variable selection. Significant predictors of vasopressor-free days included age, mechanical ventilation use, labSOFA, initial lactate value, history of liver disease, history of congestive heart failure, history of hypertension, history of end-stage renal disease, and history of chronic obstructive pulmonary disease (see Table 4). Other variables included in the model but not found to be significant included first 6-hour intravenous fluid volume, time to antibiotic administration, and biologic sex.

Sensitivity Analyses

We performed a sensitivity analysis including the patients who had an incalculable time to vasopressor initiation (n=1,815), for a total a study population of

Table 2. Bivariate of key variables and 90-day mortality.

Variables	Died (n=1,610) % (n) or Median [IQR]	Survived (n=3,089) % (n) or Median [IQR]	Effect Size [95% Confidence Interval]
Age, y	66.0 [56.5, 76.4]	60.4 [49.4, 69.8]	0.44 [0.38, 0.50]‖
Comorbid conditions			
Liver disease	31.8% (512)	17.5% (541)	0.14 [0.12, 0.17]¶
CHF	35.2% (566)	29.3% (906)	0.06 [0.03, 0.09]¶
Hypertension	63.9% (1,029)	67.1% (2,073)	−0.03 [−0.06, −0.00]¶
COPD	17.3% (278)	19.1% (591)	−0.02 [−0.04, 0.00]¶
ESRD	11.1% (178)	6.9% (213)	0.04 [0.02, 0.06]¶
HIV	2.6% (42)	2.4% (75)	0.00 [−0.01, 0.01]¶
Initial lactate value*, mmol/L	3.2 [1.8, 6.4]	2.2 [1.3, 3.7]	0.52 [0.45, 0.58]‖
LabSOFA score			
Total SOFA	3.0 [1.0, 5.0]	2.0 [1.0, 3.0]	0.51 [0.44, 0.57]‖
Renal SOFA	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.27 [0.20, 0.33]‖
Renal component (mg/dL)	1.7 [1.1, 2.9] (7 missing)	1.4 [0.9, 2.2] (27 missing)	0.14 [0.08, 0.20]‖
Hepatic SOFA	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.39 [0.33, 0.45]‖
Hepatic component (mg/dL)	0.8 [0.4, 1.9] (227 missing)	0.6 [0.4, 1.1] (717 missing)	0.35 [0.29, 0.42]‖
Coagulation SOFA	1.0 [0.0, 2.0]	0.0 [0.0, 1.0]	0.37 [0.31, 0.43]‖
Coagulation component ($10^3/\mu L$)	144.0 [83.0, 224.0] (17 missing)	173.0 [119.0, 238.0] (31 missing)	−0.21 [−0.27, −0.15]‖
Mechanical ventilation, yes	78.7% (1,267)	56.0% (1,731)	0.23 [0.20, 0.25]¶
Time to antibiotics†, Minutes	90.5 [29.3, 254.8]	115.0 [41.0, 322.0]	−0.06 [−0.12, −0.00]‖
First 6-hour‡ intravenous fluid resuscitation, milliliters	500 [0, 2,000]	500 [0, 2,000]	0.03 [−0.03, 0.10]‖
Vasopressor-free days$, d	0 [0, 0]	25 [22, 26]	−3.1 [−3.2, −3.1]‖

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; SOFA, Sequential Organ Failure Assessment score.
*267 missing.
†Winsorized.
‡First 6 hours after triage.
$Vasopressor-free days after first vasopressor initiated.
‖Cohen's D.
¶Difference in proportions.

6,514 patients with septic shock. We imputed the 39 minutes for patients who received vasopressors prior to the time of triage or without any documented hypotension or before documented hypotension. We chose 39 minutes because it was the first quartile value for time to vasopressor initiation in the original study cohort. Our results remained unchanged and we again found no significant association between time to vasopressor initiation and 90-day mortality or vasopressor-free days (see Tables E9 and E10, available at http://www.annemergmed.com). We performed a second sensitivity analysis using SBP ≤90 mmHg instead of SBP ≤100 mmHg (n=4,101; see Table E11, available at http://www.annemergmed.com). We performed a subgroup analysis to investigate whether there was an association between time to vasopressor initiation after the onset of hypotension in the subgroup of patients with an initial lactate level ≥4 mmol/L (see Table E12, available at http://www.annemergmed.com). Our results remained unchanged.

LIMITATIONS

This study had several limitations. First, it is a retrospective, observational study of patients in the OneFlorida Data Trust. Although we used a highly curated data set of electronic health record data tailored for research, data were not prospectively collected. Thus, we can only infer associations between time to vasopressor initiation and specified patient outcomes. Causality cannot be inferred from this study design, nor can this study assess whether or not vasopressors should or should not be provided to a specific patient within a certain timeline. Additionally, septic shock is dynamic and treatment is often initiated in response to evolving vital sign trends, and

Table 3. Multivariable logistic regression model for 90-day mortality.

Predictor	Coefficient	Odds Ratio	95% CI
Age	0.04	1.04	(1.04, 1.05)
Time to antibiotics	−0.00	1.00	(0.99, 1.00)
Mechanical ventilation	1.09	2.98	(2.56, 3.48)
LabSOFA score	0.17	1.18	(1.14, 1.23)
Initial lactate value	0.10	1.10	(1.08, 1.13)
History of liver disease	0.43	1.54	(1.30, 1.82)
History of CHF	0.12	1.12	(0.97, 1.30)
History of hypertension	−0.50	0.60	(0.52, 0.70)
History of ESRD	0.18	1.19	(0.94, 1.52)
History of COPD	−0.11	0.89	(0.75, 1.06)
History of HIV infection	0.37	1.45	(0.94, 2.22)
First 6-hour* intravenous fluid resuscitation	0.01	1.01	(0.97, 1.06)
Time to vasopressor initiation from first hypotensive episode	0.01	1.01	(1.00, 1.02)

*First 6 hours after time of triage.

assessment of fluid responsiveness, factors that are difficult to capture in a retrospective study. Furthermore, though a diverse state that is reasonably reflective of the country, data were limited to the state of Florida, and limit generalizability. We quantified organ failure using the laboratory components of the SOFA score, labSOFA.[27] Similar modifications of the SOFA score have been used by others with similar predictive ability for mortality.[36-38] As we have discussed previously, although we did not have pulse oximetry data to compute respiratory SOFA scores, we employed mechanical ventilation use as a surrogate for respiratory dysfunction.[27] Despite these constraints, our approach in this study of septic shock patients enabled us to consider renal, hematologic, hepatic, and respiratory dysfunction in our model.[27] Although multiple candidate variables and covariates were included in the multivariable model, some residual confounding likely exists. Lactate data were captured and included in statistical modeling, but we did not use a threshold lactate criterion for inclusion. This was an a priori decision given variation in provider ordering patterns and potential for ascertainment bias.[29,39] Other methods for abstracting patients with sepsis and septic shock may influence results.

DISCUSSION

In this large cohort of septic shock patients, we did not find time to vasopressor initiation from first hypotensive episode to be associated with 90-day mortality. Additionally, we did not find time to vasopressor initiation from first hypotensive episode to be significantly associated with vasopressor-free days. Our study included more recent data than prior studies and used advanced regression methodology to investigate relationships between the timing of vasopressor initiation and morbidity and mortality after septic shock, while controlling for other aspects of their clinical care. To our knowledge, this is one of the largest studies of vasopressor initiation timing in septic shock patients. We focused on patients started on vasopressors within the first 24 hours after triage to reflect a population of primarily community-acquired septic shock, as there are significant differences in the community-acquired and hospital-acquired sepsis populations. We measured time to vasopressor initiation from first hypotensive episode as opposed to time from triage as patients may not have been hypotensive at the time of triage. The use of triage time for time to vasopressor initiation has been the subject of critique as upward of 50% of patients with septic shock may not show evidence of septic shock at the time of triage.[40,41] We performed a sensitivity analysis, including additional patients excluded by our initial criteria, which also did not show a relationship between mortality or vasopressor-free days and time to vasopressor initiation. We performed an additional sensitivity analysis with onset of hypotension defined as the first recorded SBP measurement $\leq$90 mmHg, which also did not show a significant association with study outcomes. When limited to the subgroup of patients with an initial lactate level of 4 mmol/L or higher, we also did not find a significant relationship between mortality and time to vasopressor initiation. The strengths of our study suggest that there is unlikely an association between time to vasopressor initiation and mortality after septic shock, when assessed among a broad cohort of patients.

Heterogeneity within the septic shock population may underly the inability to identify a time-based effect among the entire cohort. Although this study did not show an association between time to vasopressor initiation and mortality among all patients in the cohort, our results raise important questions about the assumption that patients respond similarly to vasopressor therapy. There may be a subset of early responders to vasopressors, a group of patients who has improved outcomes with later timing of vasopressor initiation and more aggressive fluid resuscitation, or a group of patients who has a better trajectory with a different combination of vasopressors. The absence of an effect among the entire cohort could be explained by harm from premature vasopressors in some patients, and benefit in others who are more responsive to

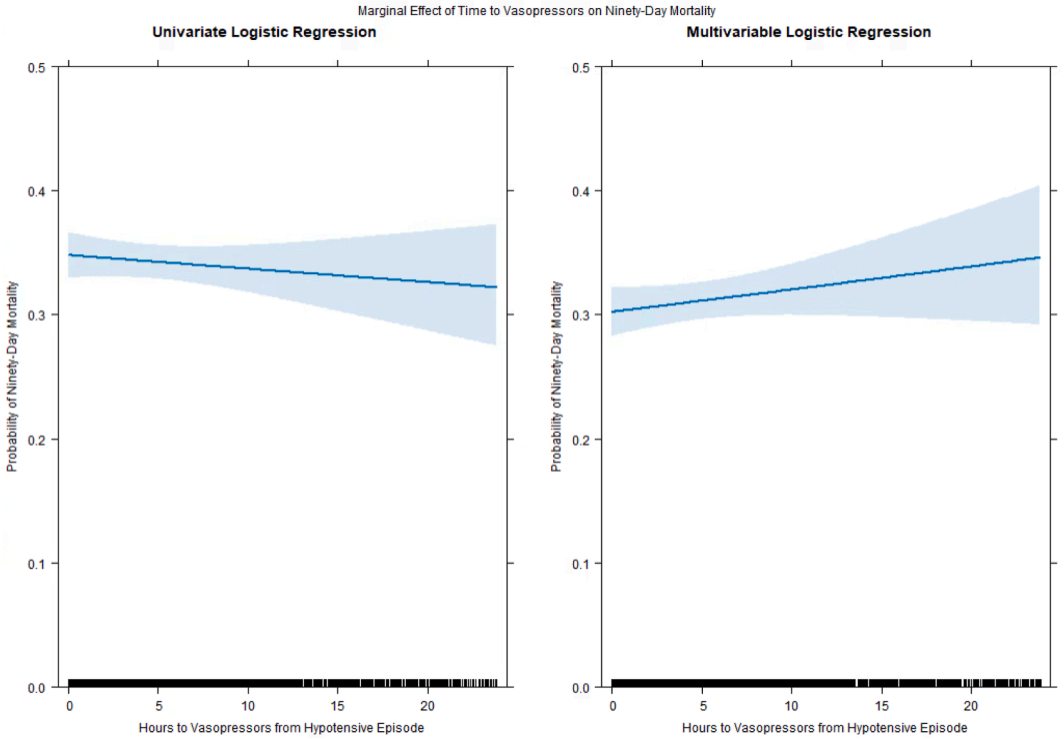

Figure. Marginal effect plots of time to vasopressor initiation and 90-day mortality. The marginal effects plots demonstrate the probability of 90-day mortality based on time to vasopressor initiation from first hypotensive episode as an unadjusted variable (univariate) and adjusted for the other variables in the model (multivariable) with shaded bands demonstrating the 95% confidence intervals. The adjusted (multivariable) marginal effects plot demonstrates the probability of 90-day mortality based on time to vasopressor initiation holding all other variables in the model at a constant value (mean for numerical values, proportionally weighted for categoric values). Without considering the covariates, the effect of increasing time to vasopressor initiation appears to have a slight (not significant) positive effect toward survival, with less confidence as the time to administration approaches 24 hours. When we consider the marginal effect of the time variable within the context of the other covariates, we see that relationship change with the general trajectory of decreased survival with increasing time to vasopressor initiation, but still not significant and with large confidence bands as the time to vasopressor initiation approaches 24 hours after first documented episode of hypotension.

Table 4. Multivariable linear regression model for vasopressor-free days.

Predictor	Coefficient	Standard Error	95% Confidence Interval
Biologic sex (female)	−0.31	0.30	(−0.89, 0.27)
Age	−0.12	0.01	(−0.14, −0.11)
Time to antibiotics	−0.01	0.01	(−0.02, 0.00)
Mechanical ventilation	−6.50	0.31	(−7.12, −5.89)
LabSOFA score	−0.88	0.08	(−1.04, −0.72)
Initial lactate value	−0.49	0.05	(−0.59, −0.40)
History of liver disease	−2.20	0.38	(−2.95, −1.45)
History of CHF	−0.70	0.33	(−1.33, −0.06)
History of hypertension	2.08	0.33	(1.44, 2.72)
History of ESRD	−1.61	0.55	(−2.69, −0.53)
History of COPD	0.60	0.39	(−0.16, 1.35)
History of HIV infection	−0.41	0.94	(−2.25, 1.44)
First 6-hour* intravenous fluid resuscitation	0.06	0.10	(−0.14, 0.25)
Time to vasopressor initiation from first hypotensive episode	−0.04	0.03	(−0.09, 0.02)

*First 6 hours after time of triage.

early vasopressors. Similarly, patients may also benefit from different blood pressure targets,[42,43] which could influence the optimal timing of vasopressor initiation. Additionally, genetic polymorphisms that influence variation in vasopressor responsiveness may inform more personalized approaches to vasopressor therapy.[44-50] Although cancer has been on the forefront of precision medicine for decades, efforts to individualize treatment are now widespread in medicine.[51] In other heterogeneous diseases, such as asthma, there has been work to tailor therapeutic interventions to phenotypes.[52] Future septic shock work should aim to identify groups of patients early in care who are likely to respond to specific therapeutic interventions so that we can provide targeted, timely, patient-centered interventions.

We have previously shown that prolonged time to vasopressor initiation was associated with increased organ failure when vasopressor initiation was delayed more than 20 hours, but we did not find that shorter delays predicted worsening organ failure.[19] Similar to our earlier findings, Beck et al[17] found increased mortality and aggregate organ failure associated only with delays in vasopressor initiation more than 14 hours. However, the Beck et al[17] study is over 15 years old and may not be relevant to current recommendations for sepsis management or expected outcomes. Our data are more recent, which allows assessment of the influence of vasopressor initiation within the contemporary management of sepsis. Some studies have found that very early vasopressor initiation may be associated with harm,[9-12] whereas others suggest that earlier vasopressor initiation may mitigate mortality.[13-17,19] Although a subset of research found no mortality difference associated with vasopressor timing,[53-56] those studies were markedly smaller than our study, most with fewer than 300 patients, increasing the likelihood of missing a clinically meaningful effect. Several studies have suggested more rapid attainment of blood pressure targets with earlier norepinephrine administration, but these studies have not consistently shown improvements in mortality.[14,15,55] Our study investigated time to vasopressor initiation a linear variable and in 2-hour intervals from the first documented episode of hypotension and did not find an association between the timing of vasopressor initiation and mortality.

Although not specifically designed to assess the adverse effects of delayed vasopressor initiation, the Crystalloid Liberal Or Vasopressors EaRly for Sepsis randomized clinical trial, which investigated restrictive fluid resuscitation with earlier vasopressor administration compared with liberal fluid resuscitation in 1,563 patients with sepsis-induced hypotension, did not find any difference in 90-day mortality, ventilator-free days, vasopressor-free days, or organ-support free days associated with earlier vasopressor initiation.[18] Among those started on vasopressors, the early vasopressor group experienced a 1.4-hour reduction in time to vasopressor initiation. Despite this, there were no differences in mortality.[18] Similarly, the Restriction of Intravenous Fluid in ICU Patients with Septic Shock randomized trial from the Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) Trial Group did not find differences in 90-day mortality among ICU patients with septic shock randomized to restricted or standard intravenous fluid resuscitation.[57] Although a randomized controlled trial of accelerated vasopressor initiation compared with usual care could provide important insights, it may confront similar challenges that have limited previous septic shock trials.

A recent meta-analysis suggested that early use of vasopressors could reduce mortality and duration of vasopressor use.[58] However, there was significant heterogeneity among the individual studies included in that meta-analysis. Specifically, most of the signal for improved outcomes was seen when investigating differences between groups of early and late vasopressor initiation; however, definitions for early and late vasopressor initiation, as well as septic shock onset, were inconsistent across the included studies. Additionally, only 4 of the 20 studies included data on the hourly association between the timing of vasopressor initiation and mortality. Among these 4 studies, there was no significant relationship between vasopressor timing and survival. Furthermore, the meta-analysis combined studies of the timing of the addition of vasopressin to norepinephrine with studies investigating time to any vasopressor, limiting the ability to generate strong conclusions from pooled data. Compared to that meta-analysis, this study was specifically designed to investigate the hourly association between the timing of vasopressor initiation from onset of hypotension and mortality and did not pool studies investigating the timing of second vasopressor initiation with the time to first vasopressor initiation.

In our study, we found age, mechanical ventilation use, labSOFA, initial lactate value, and history of liver disease to be significantly associated with increased odds of 90-day mortality. Interestingly, we found a history of hypertension to be associated with decreased odds of 90-day mortality (OR 0.60; CI 0.52 to 0.70), which may indicate opportunities for future personalized target blood pressure goals or optimization of vasopressor initiation timing. Much research has focused on the optimal blood pressure target for hypotension associated with sepsis in patients with pre-existing hypertension,[42,59] with some

others investigating the association between a history of hypertension and sepsis incidence,[60,61] but there is a scarcity of research on the association between a history of hypertension and outcomes after sepsis or septic shock. In our study, we did not find time to antibiotics to be significantly associated with improved odds of 90-day mortality; however, the median time to antibiotics was just a little over an hour and a half (105 minutes). The prompt administration of antibiotics for the entire cohort in this more recent data set of septic shock patients likely reflects change in practice since the Kumar et al[62] article, and highlights the importance of using more contemporary data for septic shock studies.

Overall, the results of our study contribute greatly to the existing literature. Although ongoing hypotension and delays in improving perfusion have been consistently associated with worse outcomes,[4-7] the timing of vasopressor administration has not yet been convincingly demonstrated to mediate that association. Future work should continue to explore heterogeneity among septic shock patients to identify subgroups of patients who may have different responses to septic shock therapies.

In summary, in this large cohort of septic shock patients, time from first hypotensive episode to vasopressor initiation was not found to be associated with 90-day mortality or vasopressor-free days. Whether there is heterogeneity in response to time to vasopressor initiation among select groups of patients remains unknown and needs continued investigation.

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