Predicting Prolonged Intensive Care Unit Stay Among Patients With Sepsis-Induced Hypotension

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Background Sepsis risk stratification tools typically predict mortality, although stays in the intensive care unit (ICU) of 24 hours or longer may be more clinically relevant for emergency department disposition.
Objective To explore predictors of ICU stay of 24 hours or longer among infected, hypotensive emergency department patients.
Methods A secondary analysis of 2 prospective, observational studies of adult patients with severe sepsis or an infection with a systolic blood pressure less than 90 mm Hg in 3 urban, academic emergency departments was performed. Patients with hypotension and infection were included. Patients with emergency department intubation, vasopressor administration, and/or death were excluded. The primary outcome was ICU stay of 24 hours or longer or death in less than 24 hours. Multivariable logistic regression was used to predict ICU stay of 24 hours or longer.
Results Of 233 patients, 108 (46.4%) had ICU stays of 24 hours or longer. History of heart failure (odds ratio, 3.6; 95% CI, 1.5-8.3), bicarbonate level less than 20 mEq/L (odds ratio, 2.0; 95% CI, 1.1-3.8), respiratory rate greater than 20/min (odds ratio, 2.0; 95% CI, 1.1-3.7), and creatinine level greater than 2.0 mg/dL (odds ratio, 3.6; 95% CI, 1.9-6.7) were independent predictors of ICU stay of 24 hours or longer (area under curve, 0.74). The presence of 1 of these factors predicted ICU stay of 24 hours or longer (area under curve, 0.74) with 82.4% sensitivity and 49.6% specificity.
Conclusions These exploratory results show that heart failure, bicarbonate level of less than 20 mEq/L, tachypnea, or creatinine level greater than 2.0 mg/dL increases the likelihood of an ICU stay of 24 hours or longer among infected, hypotensive emergency department patients.
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Sepsis, a common and deadly medical emergency, poses challenges in risk stratification and emergency department (ED) disposition. Evolving management guidelines have led to reductions in mortality via early ED resuscitation and targeted therapy,[1-3] yet predicting the clinical course and in-hospital needs of patients with sepsis is challenging. Risk stratification tools like serum lactate level and the quick Sequential Organ Failure Assessment (qSOFA) were generally calibrated to predict mortality, but they do not account for the necessary resources, including intensive care unit (ICU) resources, that may affect patient outcomes. The absence of tools to identify patients who will require ICU-specific therapies or nursing care leads to uncertainty during disposition and may contribute to prolonged ED stays because providers may delay disposition decisions in the hope of avoiding ICU admissions through resuscitation.

In the United States, ICU admission rates vary widely[4] and are influenced by a multitude of factors,[5] including poor adherence to hospital-derived ICU admission guidelines.[6] Although the mean ICU stay is 3.3 days, approximately one-third of patients do not require any active ICU monitoring or treatments (as defined by the Therapeutic Intervention Scoring System[7]) on the first day of hospitalization.[8] One hospital reported that half of the patients admitted for short ICU stays (<24 hours) did not meet their local ICU admission guidelines, receive critical care interventions, or require ICU-level nursing,[9] suggesting that a subset of ICU admissions may be avoided.

The absence of tools derived to identify which patients will require ICU-specific therapies or nursing care leads to uncertainty during disposition and may contribute to delays in admission and inefficient use of hospital resources.

This study explored clinical characteristics that may be predictors of an ICU stay of 24 hours or longer or death within 24 hours of admission among infected ED patients with hypotension. We also compared these predictors with commonly used risk stratification tools (serum lactate level and qSOFA score) that were calibrated to predict mortality in infected patients.

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Methods

We performed a retrospective secondary analysis of 2 prospective study cohorts. Both studies were approved by the institutional review board and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10]

The first study was conducted at a large, urban, academic ED in the northeastern United States with 55 000 annual visits. Researchers in that study prospectively enrolled all adult (age 18 years or older) ED patients with persistent hypotension, defined as a systolic blood pressure of less than 90 mm Hg after resuscitation with at least 1 L of intravenous fluids; a vasopressor requirement; or hypotension with intravenous fluid restriction because of a documented concern of fluid overload (ie, patients with congestive heart failure or dependent on hemodialysis). The study excluded patients with a documented baseline systolic blood pressure of less than 90 mm Hg, unless a 10 mm Hg decrease in systolic blood pressure occurred, and those who were discharged from the ED.[11] The second study was conducted in 2 urban, academic EDs in the US Pacific Northwest with 90 000 combined annual visits, and it retrospectively included all patients meeting severe sepsis criteria.[12]

The current study leveraged the 2 original data sets to create a cohort of infected patients with at least 1 systolic blood pressure reading of less than 90 mm Hg after administration of at least 1 L of intravenous fluids documented during the ED stay. All patients with nonelective intubation, vasopressor administration, and/or death in the ED were excluded because these patients have obvious requirements for ICU-level care. Patients determined by investigator adjudication to have sepsis as the

underlying cause of shock in the emergency department were included for analysis.

The screening and verification process has been described for both studies.[11,12] Medical history and the presence of altered mental status were manually abstracted from the hospital records by using a standard data collection form. Altered mental status included any mention in the ED record of altered mentation, confusion, or somnolence. Abstraction was performed by trained research assistants in the first study and by a senior emergency medicine resident in the second, all under the direct supervision of the principal investigator. Basic demographics, vital signs, length of stay, disposition, and laboratory values were obtained from the electronic health records. The primary outcome was ICU stay of 24 hours or longer or death occurring less than 24 hours after ICU admission.

We performed data analysis with statistics software (SAS 9.3, SAS Institute Inc). For continuous covariates, we used the Student *t* test and the Wilcoxon rank sum test. We created a multivariable logistic regression model to predict ICU stay of 24 hours or longer. The univariate relationships between demographics, vital signs, and laboratory study cutoffs between ICU length of stay groups were assessed with the χ^2 test for binary variables and the Student *t* test for continuous variables. We included covariates with *P* less than .10 in univariate analyses as candidate variables for the logistic regression model. We included age and serum lactate level as continuous variables and systemic inflammatory response syndrome criteria and severe sepsis organ dysfunctions as binary candidate variables a priori. We built a stepwise selection model with *P* less than .05 required for entry and *P* less than .10 required to stay in the model. The rule of 1 variable per 10 events determined the maximum number of model covariates. We assessed model discrimination with area under the curve (AUC) and model calibration with the Hosmer-Lemeshow test. We performed univariate logistic regressions for continuous qSOFA score and serum lactate level to predict ICU stay of 24 hours or longer. For the sensitivity analysis, we generated univariate logistic regression models predicting mortality using (1) any of the derived model's predictors of ICU stay of less than 24 hours, (2) stratified lactate concentrations (normal, <2.0 mmol/L; intermediate, ≥2.0 mmol/L and <4.0mmol/L; high, ≥4.0 mmol/L [divide lactate values by 0.111 to convert to mg/dL]; missing lactate values were imputed as an independent covariate), and (3) qSOFA score of 2 or less.

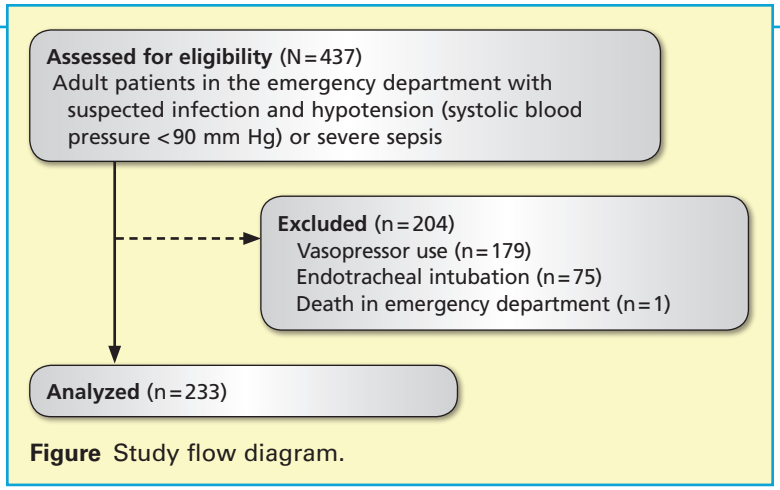

Figure Study flow diagram.

Results

Characteristics of Study Patients

The 2 original studies involved 437 patients with infectious causes of disease. We included 233 patients in our analysis (see Figure).

Age, sex, most comorbidities, and do-not-resuscitate status were similar between the 2 patient groups (those with ICU stays <24 hours and those with ICU stays ≥24 hours). Heart failure was more common among patients with ICU stays of 24 hours or longer, and chemotherapy was more common among patients with ICU stays of less than 24 hours (Table 1). Other than respiratory rate, initial vital signs were similar in the 2 groups (Table 2). Altered mental status was present in 22 of 125 patients with ICU stays of less than 24 hours (17.6%; 95% CI, 11.4%-25.4%) and in 30 of 108 patients with ICU stays of 24 or more hours (27.8%; 95% CI, 19.6%-37.2%). The mean (95% CI) ICU stays were 0.3 (0.2-0.4) days for patients with ICU stays of less than 24 hours and 3.4 (2.9-3.9) days for those with ICU stays of 24 hours or longer.

> Among patients with sepsis in the emergency department, clinical features predictive of ICU stays ≥24 hours were compared with serum lactate level and qSOFA score.

Twenty-four in-hospital deaths occurred (10.3% of patients; 95% CI, 7%-15%), all in the cohort of patients with ICU stays of 24 hours or longer. Vasopressor support was required in 6 of 125 patients with ICU stays of less than 24 hours (4.8%; 95% CI, 2%-10%) and in 25 of 108 patients with ICU stays of 24 hours or longer (23.1%; 95% CI, 16%-32%). Nonelective intubation occurred in 3 patients with ICU stays of less than 24 hours (2.4%; 95% CI, 1%-7%) and in 10 patients with ICU stays of 24 hours or more (9.3%; 95% CI, 5%-16%).

Table 1
Characteristics of patients in the study (N = 233)

Characteristic	ICU stay <24 hours (n = 125) No. (%)	95% CI	ICU stay ≥24 hours(n = 108) No. (%)	95% CI	*P*
Male sex	67 (53.6)	44.5-62.6	68 (63.0)	53.1-72.1	.15
DNR in emergency department	21 (16.8)	10.7-24.5	17 (15.7)	9.4-24.0	.83
Cardiovascular disease					
Congestive heart failure	10 (8.0)	3.9-14.2	25 (23.1)	15.6-32.2	.001
Coronary artery disease	19 (15.2)	9.4-22.7	22 (20.4)	13.2-29.2	.30
Hypertension	45 (36.0)	27.6-45.1	43 (39.8)	30.5-49.7	.55
Peripheral vascular disease	5 (4.0)	1.3-9.1	6 (5.6)	2.1-11.7	.81
Valvular heart disease	3 (2.4)	0.5-6.9	4 (3.7)	1.0-9.2	.56
Cerebrovascular accident	10 (8.0)	3.9-14.2	10 (9.3)	4.5-16.4	.73
Myocardial infarction	9 (7.2)	3.3-13.2	4 (3.7)	1.0-9.2	.25
Pulmonary disease					
Chronic obstructive pulmonary disease	15 (12.0)	6.9-19.0	14 (13.0)	7.3-20.8	.82
Hepatobiliary disease					
Liver disease	6 (4.8)	1.8-10.2	11 (10.2)	5.2-17.5	.12
Renal disease					
Chronic kidney disease	9 (7.2)	3.3-13.2	11 (10.2)	5.2-17.5	.42
End-stage renal disease	6 (4.8)	1.8-10.2	10 (9.3)	4.5-16.4	.18
Malignant neoplasm, immunosuppression					
Chemotherapy	20 (16.0)	10.1-23.6	8 (7.4)	3.3-14.1	.04
Hematologic malignant neoplasm	8 (6.4)	2.8-12.2	5 (4.6)	1.5-10.5	.56
HIV infection	3 (2.4)	0.5-6.9	2 (1.9)	0.2-6.5	.77
Cancer	41 (32.8)	24.7-41.8	31 (28.7)	20.4-38.2	.50
Metastatic cancer	11 (8.8)	4.5-15.2	8 (7.4)	3.3-14.1	.70
Transplant	6 (4.8)	1.8-10.2	5 (4.6)	1.5-10.5	.95
Other					
Indwelling urinary catheter	9 (7.2)	3.3-13.2	8 (7.4)	3.3-14.1	.95
Indwelling vascular catheter	13 (10.4)	5.7-17.1	17 (15.7)	9.4-24.0	.22
Intravenous drug abuse	3 (2.4)	0.5-6.9	7 (6.5)	2.6-12.9	.13
Dementia	8 (6.4)	2.8-12.2	7 (6.5)	2.6-12.9	.98

Abbreviations: DNR, do-not-resuscitate order; ICU, intensive care unit.

Table 2
Clinical variables

Variable	Total	ICU stay <24 hours Mean	95% CI	ICU stay ≥24 hours Mean	95% CI	*P*
Vital signs, initial						
Respiratory rate, breaths per minute	233	18.4	17.6-19.2	21.0	19.9-22.1	<.001
Heart rate, beats per minute	233	98.1	93.9-102.3	99.2	95.0-103.4	.73
Temperature, °F	233	99.3	98.9-99.7	99.2	98.8-99.6	.81
Systolic blood pressure, mm Hg	233	91.8	89.4-94.3	91.5	87.6-95.4	.89
Laboratory values						
White blood cell count, x1000/μL	229	11.8	10.2-13.4	12.7	11.2-14.1	.42
Hematocrit, %	230	34.3	33.1-35.5	32.7	31.2-34.2	.08
Platelet count, x1000/μL	229	241.2	217.5-264.9	206.5	180.7-232.4	.05
International normalized ratio	167	1.8	1.5-2.1	1.7	1.5-1.9	.60
Bicarbonate, mEq/L	229	23.6	22.7-24.5	22.0	20.9-23.2	.03
Serum urea nitrogen, mg/dL	229	26.1	22.0-30.3	38.8	33.9-43.7	<.001
Creatinine, mg/dL	229	1.5	1.2-1.7	2.2	1.8-2.5	.002
Aspartate aminotransferase, U/L	164	65.4	47.0-83.8	98.8	56.6-141.0	.15
Alanine aminotransferase, U/L	164	54.7	39.5-69.8	64.8	39.8-89.7	.49
Troponin, ng/mL	46	0.2	0.0-0.3	0.1	0.0-0.1	.21
Lactate, mmol/L	224	2.2	1.9-2.5	2.7	2.3-3.1	.03

Abbreviation: ICU, intensive care unit.
SI conversion factors: To convert serum urea nitrogen to mmol/L, multiply by 0.357. To convert creatinine to μmol/L, multiply by 88.4. To convert lactate to mg/dL, divide by 0.111.

Table 3
Multivariable logistic regression results for the 3 models[a]

Model	Covariate	AOR	95% CI	β coefficient	SE	*P*
1	Heart failure history	3.6	1.5-8.3	1.27	0.43	<.003
	Bicarbonate <20 mEq/L	2.0	1.1-3.8	0.71	0.43	.03
	Respiratory rate >20/min	2.0	1.1-3.7	0.69	0.32	.03
	Creatinine >2.0 mg/dL	3.6	1.9-6.7	1.27	0.33	<.001
2	qSOFA score	1.9	1.3-3.0	0.66	0.22	<.001
3	Lactate	1.2	1.0-1.4	0.17	0.08	.04

Abbreviations: AOR, adjusted odds ratio; qSOFA, quick Sequential Organ Failure Assessment.
[a] Area under the curve (AUC) was 0.739 for model 1 (the final model), 0.600 for the qSOFA-only model, and 0.621 for the lactate-only model. In the final study model, the Hosmer-Lemeshow Test yielded a *P* of .59.

Table 4
Multivariable logistic regression results for the final study model with the addition of history of renal disease as a potential confounder for covariate creatinine >2.0 mg/dL[a]

Covariate	AOR	95% CI	β coefficient	SE	*P*
Heart failure history	3.3	1.4-7.6	−1.20	0.43	.005
Bicarbonate <20 mEq/L	2.1	1.1-4.0	−0.74	0.33	.02
SIRS respiratory rate	1.9	1.0-3.5	−0.66	0.32	.04
Creatinine >2.0 mg/dL	4.5	2.2-9.0	−1.50	0.36	<.001
History of renal disease	0.4	0.1-1.2	0.91	0.56	.10

Abbreviations: AOR, adjusted odds ratio; CKD, chronic kidney disease; SIRS, systemic inflammatory response syndrome.
[a] Renal disease included chronic kidney disease and end-stage renal disease. Hosmer-Lemeshow test yielded a *P* value of .37.

Main Results

Of the 233 included patients, 108 (46.4%) had ICU stays of 24 hours or longer. Multivariable logistic regression identified heart failure history, bicarbonate level less than 20 mEq/L, respiratory rate greater than 20 breaths per minute, and creatinine level greater than 2.0 mg/dL as independent positive predictors of ICU stay of 24 hours or longer (Table 3). Creatinine level greater than 2.0 mg/dL remained an independent predictor ($P<.01$) when the covariate chronic kidney disease (chronic kidney disease or end-stage renal disease) was included in the model (Table 4), although a history of chronic kidney disease or end-stage renal disease was not an independent predictor ($P=.97$). No covariates were predictors of ICU stay of less than 24 hours. Of 108 patients with ICU stays of 24 hours or longer, 89 (sensitivity, 82.4%; 95% CI, 73.9%-89.1%) exhibited at least 1 of the 4 model predictors (positive likelihood ratio = 1.64). Of 125 patients without ICU stays of 24 hours or longer, 62 (specificity, 49.6%; 95% CI, 40.5%-58.7%) exhibited none of the model predictors (negative likelihood ratio = 0.35). Conversely, qSOFA score of 2 or greater had a sensitivity of 52.8% and a specificity of 65.6% for identifying patients with ICU stays of 24 hours or longer.

We compared the derived predictive factors for ICU stay of 24 hours or longer with the predictive performance of initial lactate concentration and qSOFA score. Each 1.0 mmol/L increase in serum lactate had an odds ratio of 1.2 (95% CI, 1.0-1.4) among patients with ICU stays of 24 hours or longer (AUC, 0.62; 95% CI, 0.55-0.69). Each 1-point increase in qSOFA had an odds ratio of 1.9 (95% CI, 1.3-3.0) for the primary outcome (AUC, 0.60; 95% CI, 0.54-0.66). Compared with qSOFA score and lactate level as continuous variables, the study model improved the prediction of ICU stay of 24 hours or longer (AUC, 0.74; 95% CI, 0.66-0.79). In the sensitivity analysis, the presence of a single model covariate (AUC, 0.66; 95% CI, 0.60-0.72) performed similarly to stratified lactate level (AUC, 0.60; 95% CI, 0.54-0.67) and qSOFA score of 2 or greater (AUC, 0.59; 95% CI, 0.52-0.66).

Discussion

This study sought clinical factors to predict ICU stay of 24 hours or longer among infected ED patients with hypotension. Our model, calibrated to ICU length of stay, outperformed both continuous serum lactate level and qSOFA score, suggesting that these widely known tools may not provide the most informative risk stratification when considering hospital resource needs. When applied clinically, the presence of a single model predictor demonstrated improved sensitivity for ICU stay of 24 hours or longer as compared with 2 or more qSOFA criteria. When predictors are present, early admission may be appropriate because

> Of patients with an ICU stay ≥24 hours, 82.4% exhibited at least 1 of the 4 model predictors.

prolonged ED stays (>5 hours) are associated with higher rates of ICU complications.[13] Yet in this exploratory study neither our derived model nor existing tools adequately identified patients who required ICU stays of 24 hours or longer, suggesting that further investigation is needed to assist clinicians with disposition among this subset of patients with sepsis.

Several studies have attempted to use biomarkers and adapt illness severity scores, which were derived to predict mortality, to predict ICU length of stay or ICU admission. A recent attempt to repurpose mortality-derived illness severity scores for modeling predicted ICU length of stay showed promising results.[14] However, the scoring systems used require variables not routinely captured in the ED, and the study populations were not specific to sepsis. More commonly, illness severity scores have been tested to predict ICU admission among patients without clear ICU needs (eg, those receiving vasopressors or mechanical ventilation), but the performance of scores more amenable to ED use is highly variable. The Pneumonia Severity Index and the CURB/CURB-65 (confusion, blood urea nitrogen, respiratory rate, blood pressure, age) criteria poorly predict ICU admission.[15] Among elderly patients with sepsis, the SOFA score (AUC, 0.93) and abbreviated Mortality in Emergency Department Sepsis score (AUC, 0.95) were strongly predictive of ICU admission.[16] However, other research suggests a more modest effect of SOFA score (AUC, 0.73) in predicting ICU transfer within 48 hours.[17]

Our model, calibrated to ICU length of stay, outperformed both continuous lactate level and qSOFA score.

Biomarkers in isolation perform marginally and are insufficient to predict ICU needs. For example, procalcitonin level had an AUC of 0.69 for predicting the need for vasopressor or mechanical ventilation within 72 hours of presentation[18] and is modestly outperformed by American Thoracic Society and Infectious Diseases Society of America guidelines.[19] Although a serum lactate level of greater than 4 mmol/L in patients with sepsis is a known risk factor for progression to shock and is associated with ICU admission, lactate level alone is not associated with ICU length of stay.[20] We report a similar inadequacy of serum lactate level for predicting ICU stay of 24 hours or longer. Although recent attempts to combine comorbidities and biomarkers have augmented mortality prognostication for patients with sepsis,[21] highly predictive models for ICU admission or length of stay remain elusive.

We found that qSOFA score had inadequate sensitivity and specificity for ICU stay of 24 hours or longer in this population. Although qSOFA was validated with a combination of mortality and ICU stay of longer than 3 days,[22] studies specifically regarding short ICU stay and admission disposition have not been conducted previously. The shortcomings of illness severity models, like qSOFA, are most likely related to their origin; ICU length of stay is an unintended end point for scoring systems derived to predict mortality. Calibrating predictive models for additional clinically relevant end points such as ICU stay of 24 hours or longer may be more helpful than repurposing other tools in risk-stratifying patients with sepsis.

Limitations

This report serves as a proof of principle after leveraging data sets created for a different purpose. Therefore, this secondary analysis is missing covariates that may be important for development of a clinical decision rule ready for clinical use, such as unmeasured patient, provider, and hospital-level factors that interact with ICU length of stay. We were not able to account for bed availability, although demand elasticity can affect admission disposition.[4]

Intensive care unit length of stay is an important, albeit imperfect, outcome of interest in estimating illness severity from the standpoint of ED disposition and hospital resource management. Other measures, including ICU length of stay assessed in fractions of a day, may yield more useful results, although that level of detail was not available in the data sets used. Nevertheless, using a threshold of 24 hours provides a clinically relevant outcome that clinicians may readily apply to predict inpatient resource requirements. Several implicit confounders can obscure interpretation because medical, social, psychological, and institutional factors affect ICU length of stay. For example, the delay between bed request and bed availability could be misleading because the prolongation of ICU stay reflects hospital limitations, not clinical instability.

Conclusion

In summary, a history of heart failure, serum bicarbonate level less than 20 mEq/L, tachypnea, or creatinine level greater than 2 mg/dL modestly increases the likelihood of ICU stay of 24 hours or longer in hypotensive ED patients with sepsis. Our results may have some clinical utility for patients

with the right pretest probability, but neither our model nor established tools for risk stratification currently provide adequate guidance regarding the disposition of patients who have hypotension in the context of sepsis. Our predictors represent a preliminary framework deserving further evaluation because ED disposition for sepsis is a particularly relevant outcome of interest for emergency medicine providers.

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