Factors Associated With Initiation of Mechanical Ventilation in Patients With Sepsis: Retrospective Observational Study

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Background Patients with sepsis are at risk for mechanical ventilation. This study aimed to identify risk factors for initiation of mechanical ventilation in patients with sepsis and assess whether these factors varied with time.
Methods Data from the electronic health record were used to model risk factors for initiation of mechanical ventilation after the onset of sepsis. A time-varying Cox model was used to study factors that varied with time.
Results Of 35 020 patients who met sepsis criteria, 28 747 were eligible for inclusion. Mechanical ventilation was initiated within 30 days after sepsis onset in 3891 patients (13.5%). Factors that were independently associated with increased likelihood of receipt of mechanical ventilation were race (White: adjusted hazard ratio [HR], 1.59; 95% CI, 1.39-1.83; other/unknown: adjusted HR, 1.97; 95% CI, 1.54-2.52), systemic inflammatory response syndrome (adjusted HR [per point], 1.23; 95% CI, 1.17-1.28), Sequential Organ Failure Assessment score (adjusted HR [per point], 1.28; 95% CI, 1.26-1.31), and congestive heart failure (adjusted HR, 1.30; 95% CI, 1.17-1.45). Hazard ratios decreased with time for Sequential Organ Failure Assessment score and congestive heart failure and varied with time for 4 comorbidities and 3 culture results.
Conclusions The risk for mechanical ventilation associated with different factors varied with time after sepsis onset, increasing for some factors and decreasing for others. Through a better understanding of risk factors for initiation of mechanical ventilation in patients with sepsis, targeted interventions may be tailored to high-risk patients. (*American Journal of Critical Care.* 2023; 32:358-367)

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Mechanical ventilation is frequently initiated in patients with sepsis[1-3] to maintain alveolar ventilation and arterial oxygenation. Patients with sepsis have an increased risk of hemodynamic instability,[4,5] depressed consciousness,[6-8] and sepsis-induced acute respiratory failure.[9,10] Although generally used with therapeutic intent, mechanical ventilation introduces risks that could worsen patient outcomes, and these risks increase in proportion to the duration of mechanical ventilation.[11]

Data from the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure suggest that among patients with respiratory failure receiving mechanical ventilation, those with sepsis have significantly worse outcomes than those without sepsis.[12] Risk factors including morbid obesity, increased age, electrolyte imbalance,[13] and increased Sequential Organ Failure Assessment (SOFA) score[14,15] have been associated with increased odds of requiring invasive mechanical ventilation. The decision to initiate mechanical ventilation relies on a complex interplay of patient and clinician factors and, because of limited guidelines, is ultimately left to the discretion of medical professionals. Factors that may affect this decision remain unclear, particularly in patients with sepsis.

We hypothesized that time-dependent interactions could predict the need for and timing of initiation of mechanical ventilation in patients with presumed sepsis. Time-dependent interactions are interactions whose influence increases or decreases with time. For example, a factor may be associated with early initiation of mechanical ventilation but not with mechanical ventilation that occurs several days later. A better understanding of these factors can help guide clinicians in evidence-based implementation of mechanical ventilation and in early intervention to prevent respiratory decompensation in patients at high risk for respiratory failure and mechanical ventilation.

Methods

Human Participants' Protection

The University of Michigan institutional review board approved this study (HUM00106639) and waived written informed consent because of the study's retrospective nature and deidentified data set. We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines to plan and execute this observational research study.[16]

Study Design and Population

We searched the University of Michigan Medical Center electronic health data warehouse for all patients at least 18 years of age who met the criteria of the third international consensus definitions for sepsis and septic shock. The search spanned July 10, 2009, to September 7, 2019. Patients were considered to have had sepsis if they had blood samples submitted for culture, were administered antibiotics, and had an increase in SOFA score of 2 points or greater. If an antibiotic was given before blood culture, it needed to be given within the 24 hours before the blood culture was obtained. If a blood culture was obtained first, the antibiotic needed to be given within the subsequent 72 hours. The onset of infection was determined by the time of antibiotic administration or acquisition of blood sample for culture, whichever was earlier. The increase in SOFA score by 2 points or greater needed to occur from 48 hours before to 24 hours after the onset of infection.[5]

> Patients with sepsis often require mechanical ventilation.

We excluded patients who were receiving invasive mechanical ventilation at sepsis onset, although we included patients who had received ventilation and were extubated before sepsis onset. We calculated SOFA and systemic inflammatory response syndrome (SIRS) scores according to the worst values in the 24 hours immediately before sepsis onset. We excluded patients whose times of admission, discharge, intubation, or sepsis were temporally implausible or missing.

Demographics, Elixhauser comorbidities, laboratory values, and processes of care (eg, transfusions, renal replacement therapy, and time and type of other cultures) were collected from the data warehouse. Elixhauser comorbidities, a series of

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dichotomous comorbidity categories based on *International Classification of Diseases* diagnosis codes,[17] were considered present if they were recorded before sepsis onset. Cultures were categorized either as being obtained more than 24 hours before sepsis onset or as being obtained from 24 hours before sepsis onset to 1 hour after sepsis onset. We used the limit of 1 hour after sepsis onset to allow for possible delays between ordering and collecting samples for culture. Culture results were deemed positive if a specific organism was cultured. Laboratory values at admission were those collected within 6 hours of admission. Laboratory values at sepsis onset were those obtained from 24 hours before sepsis onset to 1 hour after sepsis onset. If a laboratory value was obtained more than once during that time, the value temporally closest to sepsis onset was used.

The interaction between time from sepsis onset and risk of requiring mechanical ventilation was modeled.

Statistical Analysis

The purposeful selection process began with univariate analyses of demographic variables, baseline illness severity factors, and hospital treatment and other clinical variables to compare patients who received mechanical ventilation within 30 days after sepsis onset with patients who did not. Analyses were conducted with χ^2 and independent *t* tests for categorical and continuous variables, as appropriate. All variables were tested for multicollinearity before model construction by using a variance inflation factor of less than 4 for inclusion.[18] Continuous variables were tested for linearity by plotting Martingale residuals.[19] Variables with nonlinear associations were transformed and missing data were imputed using chained equations.[20]

Cox models were constructed by first testing the proportional hazard assumption using Schoenfeld residuals and Kaplan-Meier plots.[21] For each variable that the assumption did not hold, a time-varying interaction between that variable and linear time was created and entered in the model along with the original variable. The model was right censored for the competing risk of mortality. All variables without multicollinearity were initially considered for entry, with a stay criterion of *P* less than .05. Separate models were created for each imputed data set and combined using the Rubin rules.[22] The adjusted hazard ratios (HRs) of all significant variables remaining in the final model were reported with 95% CIs. Time-varying interactions have a baseline risk (R_0) and a risk that changes with time (R_t). To determine the risk for any day, the risk is calculated as $R_0 \times (R_t)^n$, where *n* is the number of days after the onset of sepsis. For example, for a factor with $R_0 = 2.5$ and $R_t = 0.8$, the risk on day 0 is 2.5, on day 1 is $2.5 \times 0.8 = 2.0$, and on day 2 is $2.5 \times 0.8^2 = 1.6$. The risk associated with this particular factor remains elevated (>1) until day 5, when the risk is $2.5 \times 0.8^5 = 0.8$, at which time the factor is now protective.

Post hoc logistic regressions were created to determine the factors associated with mechanical ventilation initiation (1) at any time within the 30 days after sepsis onset, (2) within only the first 24 hours after sepsis onset, and (3) from 1 through 30 days after sepsis onset but not within the first 24 hours. Likelihood ratio was used for variable selection, with a stay criterion of *P* less than .05. Separate models were created for each imputed data set and combined using the Rubin rules. The final model consisted of all variables with 95% CIs of the odds ratio that excluded 1.

All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc) and SPSS Statistics for Windows, version 27 (IBM). DataDirect (University of Michigan) was used to extract all data from the data warehouse. The University of Michigan Office of Research conducts regular ascertainments of data accuracy.

Results

A total of 35 020 patients met sepsis criteria, and 28 747 patients were eligible for inclusion in the study after we applied exclusion criteria (see Supplemental Figure, available online only at www.ajcconline.org). Of all eligible patients, 12 729 (44.3%) were female, and the 30-day mortality rate was 8.9%. Of all eligible patients, 3891 (13.5%) required mechanical ventilation within 30 days after sepsis onset. Of these 3891 patients, 2046 (52.6%) required mechanical ventilation within 24 hours after sepsis onset. Mechanical ventilation was subsequently initiated for 441 patients (11.3%) from 1 to 2 days after sepsis onset and for 312 patients (8.0%) from 2 to 3 days after sepsis onset (see Figure). The remaining 1092 patients (28.1%) experienced late respiratory failure, or invasive mechanical ventilation initiated 3 to 30 days after the onset of sepsis.

From the results of univariate comparisons of demographic variables (Supplemental Table 1, available online only), baseline illness severity factors (Supplemental Table 2, available online only), and hospital treatment and other clinical variables (Supplemental Table 3, available online only), we found

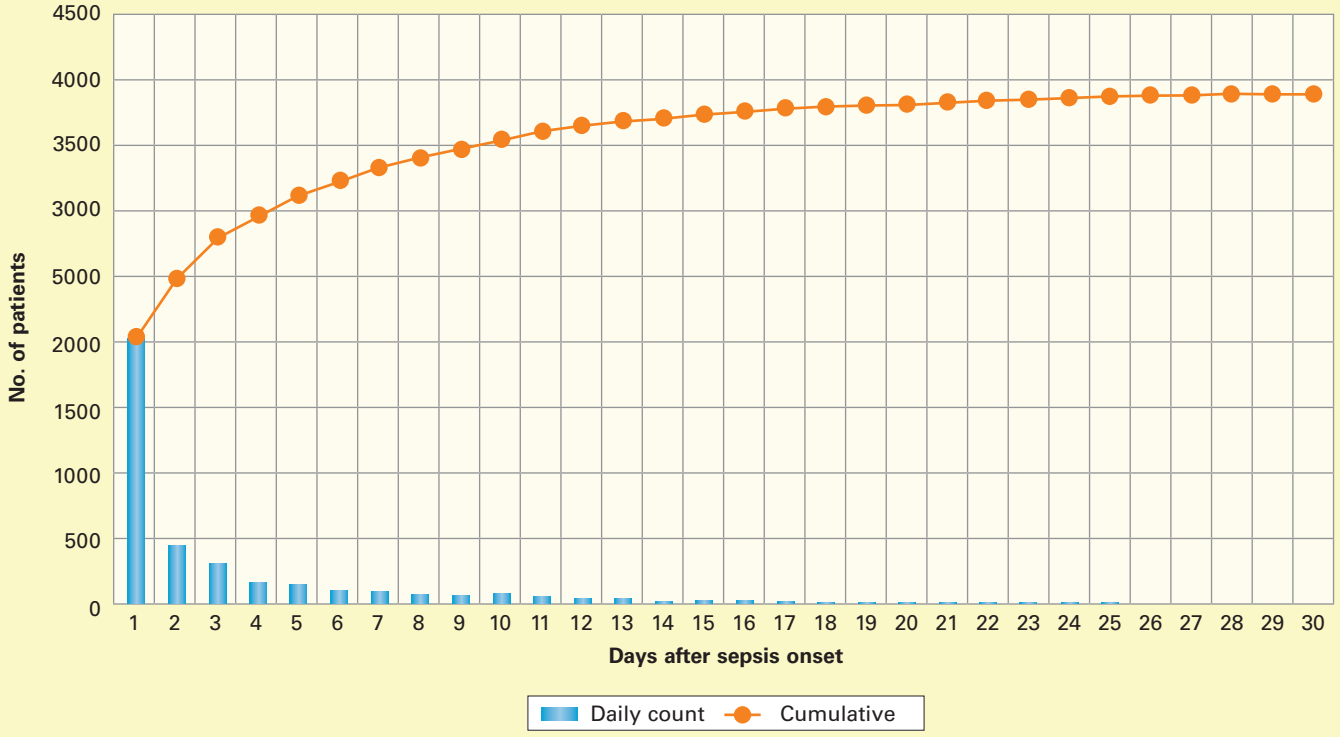

Figure The number of patients with sepsis requiring mechanical ventilation, from the date of onset of sepsis to 30 days.

that patients requiring mechanical ventilation had higher baseline illness severity than those who did not require mechanical ventilation (mean [SD] Acute Physiology and Chronic Health Evaluation II score, 7 [4] vs 5 [3]; $P<.001$) and higher in-hospital mortality (21% vs 7%; $P<.001$). In addition, patients who required mechanical ventilation had a higher prevalence of 27 of the 35 Elixhauser comorbidities (Supplemental Table 2, available online only).

Using the Cox model, we identified 6 independent risk factors associated with receiving mechanical ventilation after sepsis onset (Table 1). These factors were race, SIRS and SOFA scores, and 3 comorbidities (Supplemental Table 4, available online only). Additionally, several factors varied with time. Although the receipt of mechanical ventilation in the 14 days preceding sepsis onset was protective against mechanical ventilation after sepsis onset (adjusted HR, 0.59; 95% CI, 0.51-0.68), this protective association decreased with time (adjusted HR per day, 1.07; 95% CI, 1.05-1.09, with total HR = 0.72 by 3 days after sepsis onset and HR = 0.89 by 6 days after sepsis onset).

We performed 3 post hoc logistic regressions to further investigate the risk factors associated with intubation after sepsis onset for different time intervals. We found that septic shock, prolonged stay from admission to sepsis onset, male sex, a variety of comorbidities, and laboratory values were associated with receipt of mechanical ventilation at any time within 30 days after sepsis onset (Table 2). We compared patients who received mechanical ventilation within the first 24 hours after sepsis onset (2046 of 3891 patients [52.6%]) and patients who received mechanical ventilation starting 1 to 30 days after sepsis onset (1845 of 3891 patients [47.4%]) with patients who did not receive mechanical ventilation. After adjusting for confounders, the following were associated with receipt of mechanical ventilation within 24 hours after sepsis onset: male sex, lower SOFA score, higher SIRS score, septic shock, cardiac arrhythmias, chronic pulmonary disease, congestive heart failure, and various laboratory values (Table 3). For patients in whom mechanical ventilation was initiated 1 to 30 days after sepsis onset, risk factors included similar comorbidities but did not include male sex, SOFA score, SIRS score, and septic shock. For these patients, operation and blood transfusion before sepsis diagnosis were protective against mechanical ventilation (Table 4).

> Patients with sepsis have clear and modifiable risk factors for needing mechanical ventilation that vary with time.

We also performed a post hoc sensitivity analysis to estimate whether death without receipt of mechanical ventilation explained why mechanical

Table 1
Time-varying multivariable Cox proportional hazard model predicting the initiation of mechanical ventilation (per day)[a]

Factor	Hazard ratio	95% CI	*P*
Race			
Black	Reference	Reference	—
Asian	1.19	0.83-1.71	.34
White	1.59	1.39-1.83	<.001
Other or unknown	1.97	1.54-2.52	<.001
SIRS score (per point)	1.23	1.17-1.28	<.001
SOFA score (per point)	1.28	1.26-1.31	<.001
Time-varying interaction, SOFA score	0.99	0.98-0.99	<.001
Elixhauser comorbidity			
Elixhauser cardiac arrhythmias	1.54	1.39-1.71	<.001
Elixhauser peripheral vascular disorders	1.42	1.30-1.55	<.001
Elixhauser congestive heart failure	1.30	1.17-1.45	<.001
Time-varying interaction, Elixhauser congestive heart failure	0.87	0.85-0.89	<.001
Elixhauser diabetes complicated	1.00	1.00-1.00	—
Time-varying interaction, Elixhauser diabetes complicated	0.96	0.95-0.98	<.001
Elixhauser liver disease	1.00	1.00-1.00	—
Time-varying interaction, Elixhauser liver disease	0.95	0.93-0.97	<.001
Elixhauser paralysis	1.00	1.00-1.00	—
Time-varying interaction, Elixhauser paralysis	1.09	1.05-1.13	<.001
Elixhauser peptic ulcer disease excluding bleeding	1.00	1.00-1.00	—
Time-varying interaction, Elixhauser peptic ulcer disease excluding bleeding	1.07	1.04-1.09	<.001
Respiratory cultures sent >24 hours before sepsis	1.00	1.00-1.00	—
Time-varying interaction, respiratory cultures sent > 24 hours before sepsis	1.10	1.06-1.14	<.001
Respiratory cultures sent –1 to 24 hours before sepsis interaction	1.00	1.00-1.00	—
Time-varying interaction, respiratory cultures sent –1 to 24 hours before sepsis	1.11	1.08-1.15	<.001
Positive wound culture result >24 hours before sepsis	1.00	1.00-1.00	—
Time-varying interaction, positive wound culture result >24 hours before sepsis	1.12	1.07-1.17	<.001
Mechanical ventilation before sepsis	0.59	0.51-0.68	<.001
Time-varying interaction, mechanical ventilation before sepsis	1.07	1.05-1.09	<.001

Abbreviations: SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

[a] Factors listed as "Time-varying interaction" represent the interaction between the increasing time (in days) and the other factor. Where the time-varying interaction with the factor is statistically significant, the original factor is also displayed even with a hazard ratio (HR) equal to 1. The HR for any given day is calculated by using the formula $HR = \text{factor} \times (\text{time-varying interaction factor})^{\text{Days}}$. For example, for mechanical ventilation on day 5, $HR = 0.59 \times 1.07^5 = 0.83$.

ventilation before sepsis onset was associated with less risk of mechanical ventilation after sepsis onset. Of the 822 patients who received mechanical ventilation before but not after sepsis onset, only 35 (4%) died before hospital discharge.

Discussion

We modeled risk factors for initiation of mechanical ventilation following the documented onset of sepsis, considering that the risk associated with any factor may vary with time. Our study expands on previous studies of patients with sepsis receiving mechanical ventilation. The use of a large, granular observational data set allowed us to closely analyze important risk factors that have not been well evaluated in prior studies. The use of a time-varying Cox model added further novelty to this study because it permitted us to more closely analyze how the risk factors for initiation of mechanical ventilation may change over time.

We found that 13.5% of patients with a new diagnosis of sepsis required initiation of mechanical ventilation. Of these, 52.6% required mechanical ventilation within the first 24 hours after sepsis onset, consistent with prior work on this topic.[13,23,24] However, nearly half of mechanical ventilation initiations (47.4%) occurred after 24 hours, and 28.1% of patients with sepsis required mechanical ventilation initiation more than 3 days after sepsis onset, indicating that sepsis is associated with delayed respiratory decompensation. Given that mechanical ventilation is costly, prolongs hospital stays, and is associated with increased mortality, efforts to identify patients at high risk and implement targeted interventions in a timely manner offer the potential to significantly improve outcomes.[14,25]

We found that the risk factors for mechanical ventilation vary with time. The deleterious associations from acute organ derangements, characterized by higher SOFA scores, rapidly resolve (as shown by time-varying HRs of less than 1) and have little to no effect on later initiation of mechanical ventilation. We also identified potentially modifiable factors associated with later initiation. Fluid overload has been shown to be a risk factor for intubation,[26] yet fluid resuscitation to maintain intravascular volume and optimize cardiac output is the mainstay of sepsis therapy.[3] More judicious fluid administration or earlier diuresis may decrease respiratory failure without compromising resuscitation. Similarly, patients with coagulopathies are frequently treated with large volumes of blood components. Further studies of alternatives to large volumes of plasma, such as vitamin K, andexanet alfa, or prothrombin complex concentrate, should be conducted.

Other risk factors for later mechanical ventilation include respiratory tract culture after sepsis onset and mechanical ventilation before sepsis onset. Prospective studies of patients with new diagnoses of sepsis who have these risk factors might include earlier administration of noninvasive ventilation or heated high-flow nasal oxygen to decrease receipt of mechanical ventilation. Although mechanical ventilation before sepsis onset was initially protective (HR = 0.63 on day 1), by day 9 it was associated with an increased risk of new mechanical ventilation (HR = 1.08 on day 9 and HR = 2.28 on day 20). However, as the number of patients receiving mechanical ventilation decreased over time, the absolute risk associated with mechanical ventilation before sepsis onset decreased. Conversely, the HRs for SOFA score, congestive heart failure, complicated diabetes, and liver disease all decreased with time, suggesting that patients who do not receive mechanical ventilation within the first 24 hours after sepsis onset are increasingly less likely to receive it in subsequent days. Studies are needed to determine why these associated risks decrease or increase with time and how physicians can modify these risks to improve outcomes.

Our results agree with those of previous studies that found SOFA score to be associated with adverse outcomes[14,15,27,28] and extend those findings by showing a time-varying association indicating that the harmful association with SOFA score wanes over time. Our logistic regression model confirmed this finding, demonstrating that a higher SOFA score was associated with receipt of mechanical ventilation within the first 24 hours after sepsis onset but not with later initiation of mechanical ventilation.

Table 2
Logistic regression model of mechanical ventilation initiation any time within 30 days after sepsis onset[a]

Variable	Odds ratio	95% CI	*P*
Prolonged stay from admission to sepsis (d)	1.02	1.01-1.02	<.001
Age (y)	0.99	0.99-1.00	<.001
Septic shock	1.49	1.19-1.86	<.001
Insurance			<.001
Medicare	Reference	Reference	
Other governmental	0.94	0.82-1.07	.32
Other, unknown, or none	1.42	1.29-1.56	<.001
Private	1.04	0.94-1.16	.44
Height (cm)	1.00	0.99-1.00	.03
Weight (kg)	1.00	1.00-1.01	<.001
Male sex	1.15	1.05-1.25	.003
Elixhauser comorbidities			
Blood loss anemia	1.23	1.08-1.40	.002
Cardiac arrhythmias	1.91	1.75-2.09	<.001
Chronic pulmonary disease	1.22	1.12-1.32	<.001
Coagulopathy	1.49	1.37-1.62	<.001
Congestive heart failure	1.61	1.47-1.76	<.001
Deficiency anemia	0.80	0.73-0.89	<.001
Depression	0.85	0.79-0.92	<.001
Diabetes uncomplicated	0.82	0.75-0.90	<.001
Fluid electrolyte disorders	1.64	1.50-1.80	<.001
Hypertension complicated	0.67	0.60-0.74	<.001
Lymphoma	0.74	0.64-0.85	<.001
Metastatic cancer	0.67	0.62-0.74	<.001
Other neurological disorders	1.40	1.29-1.53	<.001
Paralysis	1.43	1.25-1.65	<.001
Peptic ulcer disease excluding bleeding	1.16	1.01-1.33	.03
Peripheral vascular disorders	1.28	1.17-1.39	<.001
Psychoses	0.80	0.69-0.93	.004
Pulmonary circulation disorders	1.21	1.11-1.33	<.001
Renal failure	1.17	1.06-1.28	.001
Rheumatoid arthritis collagen vascular diseases	0.86	0.76-0.96	.009
Valvular disease	1.22	1.11-1.34	<.001
Presepsis transfusion	0.73	0.62-0.86	<.001
Admission laboratory value			
Lactate (mmol/L)	1.07	1.04-1.10	<.001
Sepsis laboratory value			
Sodium (mEq/L)[b]	1.01	1.00-1.02	.005
White blood cell count (×1000/μL)[b]	1.01	1.00-1.01	<.001
Platelet count (×1000/μL)[b]	1.00	1.00-1.00	<.001
Bicarbonate (mEq/L)[b]	1.05	1.04-1.06	<.001
Calcium (mg/dL)[b]	1.06	1.04-1.07	<.001
Phosphorus (mg/dL)[b]	1.08	1.04-1.11	<.001
Albumin (g/dL)[b]	1.53	1.44-1.63	<.001
INR	0.90	0.86-0.95	<.001
Glucose (mg/dL)[b]	1.13	1.06-1.20	<.001
Lactate (mmol/L)	1.06	1.03-1.09	<.001
Cultures sent >24 hours before sepsis onset			
Unknown source	2.69	1.61-4.49	<.001
Cultures sent <24 hours before sepsis onset			
Respiratory	2.00	1.68-2.38	<.001
Urine	1.11	1.03-1.20	.009
Body fluid	0.77	0.63-0.95	.02
Unknown source	2.69	1.61-4.49	<.001
Positive results for cultures sent >24 hours before sepsis onset			
Blood	0.51	0.34-0.78	.002
Wound	0.57	0.37-0.90	.02
Urine	0.70	0.56-0.89	.004

Continued

Table 2
Continued

Variable	Odds ratio	95% CI	*P*
Positive results for cultures sent <24 hours before sepsis onset			
Blood	1.70	1.43-2.02	<.001
Constant	0.03	—	<.001

Abbreviation: INR, international normalized ratio.

[a] C statistic = 0.77 ± 0.00, *P* < .001.
[b] The odds ratios for laboratory values that were transformed to linear values are for each 1-point increase in the transformed values. Values were transformed as transformed value = |value − median of the reference range|, where |*x*| is the absolute value of *x*: for sodium |*x* − 140|, white blood cell count |*x* − 7.75|, platelet count |*x* − 275|, bicarbonate |*x* − 25|, calcium |*x* − 9.5|, phosphorus |*x* − 3.5|, albumin |*x* − 4.4|, and glucose |*x* − 100|. For example, the odds ratio for sodium levels of both 130 mEq/L and 150 mEq/L is $(1.01)^{10} = 1.10$.

Our findings demonstrate that patients with sepsis are at particular risk for mechanical ventilation and that once mechanical ventilation is initiated, these patients experience a high mortality rate. Although prior studies identified some of the same risk factors, including morbid obesity, increased age, male sex, hyperkalemia, and hypernatremia, these studies used data sources with significantly less granularity than ours and did not differentiate between risk factors occurring before and after the onset of sepsis.[13] We extended and improved upon these findings by using only data present at or before sepsis onset and by evaluating other clinically relevant variables that are not available in large, publicly available data sets. These variables include risk factors known upon admission, those available before the onset of sepsis, and important determinants available to clinicians at the time of sepsis onset. Identifying risk factors allows physicians and nurses to distinguish patients with potential risk. Future studies are needed to determine if intubation rates can be decreased by treating high-risk patients with modalities such as noninvasive ventilation or heated high-flow oxygen or by paying closer attention to fluid status in patients with congestive heart failure.

Patients with sepsis are dynamic, and risk of respiratory failure may increase or decrease with time.

Limitations of this study deserve further elaboration. Noninvasive ventilation and high-flow nasal cannula use may have decreased the need for intubation and mechanical ventilation and could have affected our models. We chose the time of sepsis documentation as the most relevant time frame for modeling because we felt that at that time patients might be easily identified as being at high risk and therefore targets for intervention with rescue modalities such as bilevel positive airway pressure and high-flow nasal cannula use.[29-31] Although laboratory values and SOFA scores vary with time, we based the analyses on these values at the time of sepsis onset. Using values recorded earlier or later or repeated values might have produced different results. We did not analyze processes of care that may have varied over the course of this study, and the reasons for intubation were not available. Despite these limitations, the logistic regression models had good discrimination, suggesting that the variables we identified contributed a significant portion of the reasons for receipt of mechanical ventilation. Further studies are needed to determine the effects of fluid resuscitation and other processes of care on receipt of mechanical ventilation. Although a variety of methods can be used for variable selection (eg, the Akaike information criterion and the least absolute shrinkage and selection operator), we based variable selection on likelihood ratios as outlined by Hosmer and Lemeshow.[32]

Although a time-varying Cox model offers flexibility in assessing the effects of temporal elements, we analyzed only linear time. Including other functions of time, such as logarithmic time or time with an exponential decay, might have improved the fit of the model by finding nonlinear associations, but doing so was not computationally feasible for us. More complicated models are also more difficult for clinicians to interpret. Including several time functions may misidentify associations as being time varying, and the power and discrimination ability of tests can be reduced over time because of an inferior model fit.[33,34]

The results of this single-institution study, conducted at a hospital with high percentages of patients admitted for surgery and for tertiary referrals, are not generalizable to hospitals that admit a higher percentage of patients for medical treatment or that have more community admissions. Future work should assess the generalizability of our models.

Conclusions

The strengths of this study were the large sample of medical and surgical patients and the highly granular data, which allowed us to assess a wide variety of variables when selecting variables for the models. Our use of a time-varying Cox model is particularly useful to clinicians because risk factors may vary at different time points. The temporal dynamics of covariate effects are ignored in many models; models often predict that an adverse event will occur at some point without offering insight into when.

We used a time-varying model to identify factors associated with the initiation of mechanical ventilation in patients within 30 days after sepsis onset. Future studies are needed to determine how best to improve

clinical care for patients with sepsis who might need mechanical ventilation.

FINANCIAL DISCLOSURES
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SEE ALSO

For more about patients with sepsis, visit the *Critical Care Nurse* website, **www.ccnonline.org**, and read the article by Semanco et al, "Improving Initial Sepsis Management Through a Nurse-Driven Rapid Response Team Protocol" (October 2022).

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Table 3
Logistic regression model of mechanical ventilation initiation within the first 24 hours after sepsis onset[a]

Variable	Odds ratio	95% CI	*P*
SOFA score	0.96	0.93-0.99	.005
SIRS score	1.08	1.01-1.15	.03
Septic shock	2.12	1.64-2.75	<.001
Insurance			<.001
Medicare	Reference	Reference	
Other governmental	0.99	0.84-1.16	.86
Other, unknown, or none	1.31	1.16-1.48	<.001
Private	1.03	0.90-1.17	.71
Height (cm)	0.99	0.99-1.00	.003
Weight (kg)	1.00	1.00-1.01	<.001
Male	1.23	1.10-1.38	<.001
Elixhauser comorbidities			
Cardiac arrhythmias	1.80	1.60-2.02	<.001
Chronic pulmonary disease	1.27	1.15-1.40	<.001
Congestive heart failure	1.36	1.21-1.53	<.001
Diabetes uncomplicated	0.76	0.67-0.85	<.001
Fluid electrolyte disorders	1.49	1.32-1.67	<.001
Hypertension complicated	0.67	0.60-0.76	<.001
Lymphoma	0.68	0.56-0.82	<.001
Metastatic cancer	0.77	0.69-0.86	<.001
Other neurological disorders	1.39	1.25-1.55	<.001
Paralysis	1.49	1.26-1.77	<.001
Peripheral vascular disorders	1.25	1.12-1.39	<.001
Valvular disease	0.87	0.77-0.99	.03
Admission laboratory value			
Lactate (mmol/L)	1.08	1.04-1.11	<.001
Sepsis laboratory value			
Potassium (mEq/L)[b]	1.22	1.10-1.35	<.001
Sodium (mEq/L)[b]	1.01	1.00-1.03	.02
White blood cell count (×1000/μL)[b]	1.00	1.00-1.01	<.001
Platelet count (×1000/μL)[b]	1.00	1.00-1.00	<.001
Bicarbonate (mEq/L)[b]	1.06	1.04-1.07	<.001
Calcium (mg/dL)[b]	1.06	1.03-1.08	<.001
Phosphorus (mg/dL)[b]	1.14	1.10-1.19	<.001
Albumin (g/dL)[b]	1.20	1.08-1.33	.001
Total protein (g/dL)[b]	1.18	1.09-1.27	<.001
Lactate (mmol/L)	1.10	1.07-1.14	<.001
INR	0.93	0.87-0.99	.03
Glucose (mg/dL)[b]	1.21	1.13-1.30	<.001
Cultures sent >24 hours before sepsis onset			
Urine	0.83	0.71-0.98	.03
Cultures sent <24 hours before sepsis onset			
Respiratory	1.77	1.42-2.21	<.001
Body fluid	0.65	0.48-0.87	.004
Unknown source	3.13	1.75-5.62	<.001
Positive results for cultures sent >24 hours before sepsis onset			
Blood	0.26	0.12-0.55	<.001
Respiratory	1.88	1.05-3.40	.04
Positive results for cultures sent <24 hours before sepsis onset			
Blood	1.58	1.39-1.80	<.001
Constant	0.02	—	<.001

Abbreviations: INR, international normalized ratio; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

[a] C statistic = 0.77 ± 0.01, $P < .001$.
[b] The odds ratios for laboratory values that were transformed to linear values are for each 1-point increase in the transformed values. Values were transformed as transformed value = |value − median of the reference range|, where |*x*| is the absolute value of *x*: potassium |*x* − 4.25|, sodium |*x* − 140|, white blood cell count |*x* − 7.75|, platelet count |*x* − 275|, bicarbonate |*x* − 25|, calcium |*x* − 9.5|, phosphorous |*x* − 3.5|, albumin |*x* − 4.4|, total protein |*x* − 7.1|, and glucose |*x* − 100|. For example, the odds ratio for sodium levels of both 130 mEq/L and 150 mEq/L is $(1.01)^{10} = 1.15$.

Table 4
Logistic regression model of mechanical ventilation initiation from 1 through 30 days after sepsis onset[a]

Variable	Odds ratio	95% CI	*P*
Prolonged stay from admission to sepsis (d)	1.02	1.01-1.03	<.001
Age (y)	0.99	0.99-0.99	<.001
Insurance			<.001
Medicare	Reference	Reference	—
Other governmental	0.88	0.73-1.06	.17
Other, unknown, or none	1.45	1.27-1.65	<.001
Private	1.05	0.91-1.21	.53
Weight (kg)	1.00	1.00-1.01	.002
Elixhauser comorbidities			
Blood loss anemia	1.33	1.12-1.57	.001
Cardiac arrhythmias	1.96	1.72-2.24	<.001
Chronic pulmonary disease	1.12	1.00-1.26	.049
Coagulopathy	1.84	1.65-2.07	<.001
Congestive heart failure	1.84	1.62-2.09	<.001
Deficiency anemia	0.72	0.63-0.83	<.001
Depression	0.80	0.71-0.89	<.001
Drug abuse	0.80	0.66-0.97	.02
Fluid electrolyte disorders	1.75	1.54-2.00	<.001
Hypertension complicated	0.72	0.62-0.82	<.001
Lymphoma	0.82	0.68-0.99	.04
Metastatic cancer	0.61	0.54-0.69	<.001
Other neurological disorders	1.33	1.18-1.49	<.001
Paralysis	1.32	1.08-1.62	.007
Peptic ulcer disease excluding bleeding	1.25	1.04-1.50	.02
Peripheral vascular disorders	1.29	1.15-1.45	<.001
Psychoses	0.77	0.62-0.96	.02
Pulmonary circulation disorders	1.38	1.22-1.56	<.001
Renal failure	1.33	1.17-1.52	<.001
Rheumatoid arthritis collagen vascular diseases	0.76	0.65-0.90	.001
Valvular disease	1.60	1.42-1.81	<.001
Presepsis transfusion	0.72	0.58-0.89	.003
Operation	0.75	0.65-0.87	<.001
Admission laboratory value			
Lactate (mmol/L)	1.03	1.00-1.06	.04
Sepsis laboratory value			
Potassium (mEq/L)[b]	0.82	0.72-0.93	.002
White blood cell count (×1000/μL)[b]	1.01	1.00-1.01	<.001
Platelet count (×1000/μL)[b]	1.00	1.00-1.00	.001
Bicarbonate (mEq/L)[b]	1.03	1.01-1.04	.002
Calcium (mg/dL)[b]	1.06	1.03-1.08	<.001
Albumin (g/dL)[b]	1.62	1.48-1.77	<.001
Partial thromboplastin time (s)[b]	1.01	1.00-1.02	.002
INR	0.84	0.78-0.91	<.001
Bilirubin (mg/dL)	1.03	1.02-1.04	<.001
Cultures sent <24 hours before sepsis onset			
Respiratory	1.96	1.56-2.46	<.001
Urine	1.19	1.06-1.34	.003
Positive results for cultures sent >24 hours before sepsis onset			
Body fluid	1.66	1.00-2.76	.05
Urine	0.59	0.42-0.83	.003
Positive results for cultures sent <24 hours before sepsis onset			
Urine	0.70	0.56-0.88	.002
Constant	0.01	—	<.001

Abbreviation: INR, international normalized ratio.

[a] C statistic = 0.79±0.00, $P<.001$.

[b] The odds ratios for laboratory values that were transformed to linear values are for each 1-point increase in the transformed values. Values were transformed as transformed value=|value−median of the reference range|, where |x| is the absolute value of x: potassium $|x-4.25|$, white blood cell count $|x-7.75|$, platelet count $|x-275|$, bicarbonate $|x-25|$, calcium $|x-9.5|$, albumin $|x-4.4|$, and partial thromboplastin time $|x-30|$. For example, the odds ratio for both a bicarbonate level of 30 mEq/L and a bicarbonate level of 20 mEq/L is $(1.03)^5=1.16$.

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CE 1.0 Hour Category A

Notice to CE enrollees:

This article has been designated for CE contact hour(s). The evaluation demonstrates your knowledge of the following objectives:

1. Identify risk factors for patients with sepsis to require mechanical ventilation.
2. Describe how risk factors vary with time.
3. Analyze how to incorporate these findings into your clinical practice.

To complete the evaluation for CE contact hour(s) for activity A2351, visit https://aacnjournals.org/ajcconline/ce-articles. No CE fee for AACN members. See CE activity page for expiration date.

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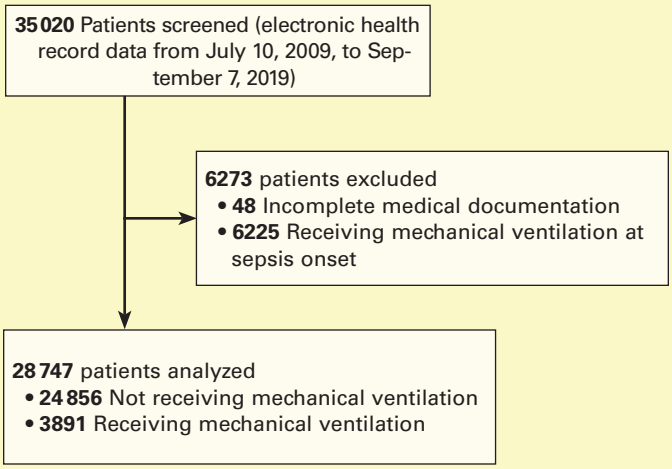

Supplemental Figure Flowchart of selection of patients for inclusion in the study.

Supplemental Table 1

Univariate comparisons of demographic variables between patients with and without mechanical ventilation

Variable	No ventilation (n=24 856)	Ventilation (n=3891)	*P*
Age, mean (SD), y	60 (17)	60 (16)	.36
Height, mean (SD), cm	170 (14)	170 (13)	.15
Weight, mean (SD), kg	84.6 (25.4)	86.9 (28.1)	<.001
Body mass index,[a] mean (SD)	28.9 (7.4)	29.3 (7.8)	.002
Female sex, No. (%) of patients	11 145 (45)	1584 (41)	<.001
Marital status, No. (%) of patients			
Married	12 575 (51)	1898 (49)	.04
Unmarried	10 302 (41)	1664 (43)	.12
Unknown	1979 (8)	329 (8)	.31
Race, No. (%) of patients			
White	20 504 (83)	3165 (81)	.08
Black	2751 (11)	471 (12)	.06
Other or unknown	1601 (6)	255 (7)	.82
Insurance, No. (%) of patients			
Medicaid	2484 (10)	409 (11)	.33
Medicare	8190 (33)	1155 (30)	<.001
Private	7477 (30)	938 (24)	<.001
All other	517 (2)	97 (3)	.11
Unknown	6188 (25)	1292 (33)	<.001
Mechanical ventilation before sepsis, No. (%) of patients[b]	821 (3)	210 (5)	<.001
Time from admission to sepsis, mean (SD), d	2.3 (4.7)	2.7 (5.9)	<.001
30-day mortality, No. (%) of patients	1752 (7)	808 (21)	<.001

[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Patients who had received mechanical ventilation in the 14 days preceding sepsis onset but had been extubated before sepsis onset.

Supplemental Table 2

Univariate comparisons of baseline illness severity factors between patients with and without mechanical ventilation

Variable	No ventilation (n=24 856)	Ventilation (n=3891)	*P*
APACHE II score, mean (SD)	5 (3)	7 (4)	<.001
Admission laboratory values, mean (SD)			
Potassium, mEq/L	4.3 (0.7)	4.4 (0.8)	<.001
Sodium, mEq/L	137 (5)	136 (6)	<.001
Bicarbonate, mEq/L	25 (4)	25 (5)	<.001
Chloride, mEq/L	103 (6)	102 (7)	<.001
Urea nitrogen, mg/dL	28 (22)	35 (26)	<.001
Creatinine, mg/dL	1.6 (1.6)	1.8 (1.7)	<.001
Calcium, mg/dL	8.1 (2.1)	7.8 (2.2)	<.001
Phosphorus, mg/dL	3.7 (1.3)	4 (1.6)	<.001
Hemoglobin, g/dL	11.4 (2.5)	11.3 (2.7)	.12
White blood cell count, ×1000/μL	12.1 (19.1)	15.2 (25.7)	<.001
Platelet count, ×1000/μL	203 (127)	210 (125)	<.001
Albumin, g/dL	3.6 (0.6)	3.4 (0.7)	<.001
Total protein, g/dL	6.4 (0.9)	6.1 (1.1)	<.001
Prothrombin time, s	14 (7.9)	15.5 (9.7)	<.001
Bilirubin, mg/dL	1.6 (3.8)	2.2 (5.1)	<.001
ALT, U/L	76 (385)	145 (661)	<.001
AST, U/L	94 (516)	209 (1054)	<.001
Glucose, mg/dL	136 (71)	144 (82)	<.001
Lactate, mmol/L	2 (1.7)	2.8 (2.7)	<.001
Elixhauser comorbidities, No. (%) of patients			
AIDS/HIV	215 (1)	24 (1)	.14
Alcohol abuse	2122 (9)	469 (12)	<.001
Anemia, blood loss	1671 (7)	410 (11)	<.001
Anemia, deficiency	4081 (16)	726 (19)	<.001
Cardiac arrhythmias	14 446 (58)	3097 (80)	<.001
Cerebrovascular disease	4938 (20)	1062 (27)	<.001
Chronic pulmonary disease	8875 (36)	1773 (46)	<.001
Coagulopathy	7824 (31)	1792 (46)	<.001
Congestive heart failure	6729 (27)	1783 (46)	<.001
Dementia	1038 (4)	135 (3)	.04
Depression	8118 (33)	1243 (32)	.39
Diabetes with chronic complications	3859 (16)	684 (18)	.001
Diabetes without chronic complications	7954 (32)	1341 (34)	.002
Drug abuse	2084 (8)	365 (9)	.04
Fluid electrolyte disorders	14 598 (59)	3065 (79)	<.001
Hypertension complicated	6725 (27)	1239 (32)	<.001
Hypertension uncomplicated	15 428 (62)	2589 (67)	<.001
Hypothyroidism	4512 (18)	736 (19)	.26
Liver disease, mild	6525 (26)	1198 (31)	<.001
Liver disease, moderate or severe	2300 (9)	487 (13)	<.001
Lymphoma	2948 (12)	293 (8)	<.001
Malignancy, metastatic	8702 (35)	935 (24)	<.001
Malignancy, nonmetastatic	1658 (7)	251 (6)	.63
Myocardial infarction	3727 (15)	943 (24)	<.001
Obesity	6904 (28)	1199 (31)	<.001
Other neurological disorder	5081 (20)	1209 (31)	<.001
Paralysis	1568 (6)	351 (9)	<.001
Peptic ulcer disease	1959 (8)	432 (11)	<.001
Peripheral vascular disease	6864 (28)	1459 (37)	<.001
Psychoses	1608 (6)	248 (6)	.85
Pulmonary circulation disorders	4919 (20)	1215 (31)	<.001
Renal disease	9320 (37)	1774 (46)	<.001
Rheumatic disease	3090 (12)	450 (12)	.13
Valvular disease	4611 (19)	1166 (30)	<.001
Weight loss	7176 (29)	1305 (34)	<.001

Abbreviations: ALT, alanine aminotransferase; APACHE, physiology portion of the Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase.

Supplemental Table 3
Univariate comparisons of hospital treatment and other clinical variables between patients with and without mechanical ventilation

Variable	No ventilation (n=24 856)	Ventilation (n=3891)	*P*
Renal replacement therapy before sepsis, No. (%) of patients	672 (3)	183 (5)	<.001
Red blood cell transfusion before sepsis, No. (%) of patients	1424 (6)	181 (5)	.007
Plasma transfusion before sepsis, No. (%) of patients	1518 (6)	183 (5)	<.001
Platelet transfusion before sepsis, No. (%) of patients	1369 (6)	161 (4)	<.001
Cryoprecipitate transfusion before sepsis, No. (%) of patients	1557 (6)	202 (5)	.01
SOFA score,[a] mean (SD)			
Nervous system	0.0 (0.0)	0.1 (0.1)	.21
Liver	0.9 (0.2)	0.4 (1.0)	<.001
Kidney	0.6 (1.0)	0.8 (1.1)	<.001
Coagulation	0.8 (1.2)	0.7 (1.1)	<.001
Cardiovascular	0.1 (0.5)	0.3 (0.8)	<.001
Respiratory	0.2 (0.6)	0.5 (1.1)	<.001
Cultures sent at sepsis onset, No. (%) of patients			
Blood	24 856 (100)	3891 (100)	>.99
Cerebrospinal fluid	157 (1)	22 (1)	.70
Respiratory	737 (3)	218 (6)	<.001
Wound	517 (2)	55 (1)	.007
Urine	8725 (35)	1438 (37)	.03
Other body fluid	796 (3)	120 (3)	.73
Unknown type	67 (0)	26 (1)	<.001
Sepsis laboratory values, mean (SD)			
Potassium, mEq/L	4.2 (0.6)	4.2 (0.7)	<.001
Sodium, mEq/L	137 (5)	136 (6)	<.001
Bicarbonate, mEq/L	25 (4)	24 (5)	<.001
Chloride, mEq/L	103 (6)	103 (7)	<.001
Urea nitrogen, mg/dL	28 (22)	36 (26)	<.001
Creatinine, mg/dL	1.5 (1.6)	1.8 (1.7)	<.001
Calcium, mg/dL	7.5 (2.5)	7 (2.6)	<.001
Phosphorus, mg/dL	3.6 (1.4)	4 (1.8)	<.001
Hemoglobin, g/dL	27.9 (10.2)	27.2 (10.4)	<.001
White blood cell count, ×1000/μL	11.6 (15.7)	15.2 (23.5)	<.001
Platelet count, ×1000/μL	192 (131)	205 (129)	<.001
Albumin, g/dL	3.5 (0.6)	3.2 (0.7)	<.001
Total protein, g/dL	6.2 (1)	6 (1.1)	<.001
Prothrombin time, s	14.3 (7.9)	15.4 (9.2)	<.001
Bilirubin, mg/dL	1.8 (3.9)	2.5 (5.4)	<.001
ALT, U/L	85 (398)	154 (652)	<.001
AST, U/L	94 (516)	209 (1054)	<.001
Glucose, mg/dL	134 (63)	145 (67)	<.001
Lactate, mmol/L	1.9 (1.6)	2.7 (2.6)	<.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOFA, Sequential Organ Failure Assessment.

[a] SOFA scores for prediction of future ventilator status were based on SOFA scores at the time of suspected sepsis onset, not the wider time window permitted by Sepsis-3 definition. If a patient were intubated 12 hours after sepsis onset, the SOFA score for respiratory system would worsen. It would be inappropriate to use this score to predict intubation.

Supplemental Table 4
Variables included in time-dependent coefficient Cox model

Covariates included in the Cox model with time-varying coefficients and in the logistic regressions were time from admission to sepsis onset, age, sex, race, height, weight, SIRS score, SOFA score, physiology portion of the APACHE 2 score, septic shock, insurance status, prior mechanical ventilation, renal replacement therapy, blood transfusion (red blood cells, platelets, plasma, or cryoprecipitate), operation, laboratory values at both admission and sepsis onset (lactate, transformed sodium, transformed potassium, transformed chloride, transformed bicarbonate, urea nitrogen, creatinine, transformed glucose, transformed calcium, transformed phosphorus, transformed albumin, transformed total protein, AST, ALT, bilirubin, hemoglobin, transformed white blood cell count, transformed platelet count, transformed red blood cell distribution width, international normalized ratio of prothrombin time, transformed partial thromboplastin time), cultures (blood, respiratory, urine, wound, cerebrospinal fluid, other body fluid, unknown type) obtained > 24 hours before sepsis onset, cultures (blood, respiratory, urine, wound, cerebrospinal fluid, other body fluid, unknown type) obtained between 24 hours before sepsis onset and 1 hour after sepsis onset, positive results for cultures (blood, respiratory, urine, wound, cerebrospinal fluid, other body fluid, unknown type) obtained >24 hours before sepsis onset, positive results for cultures (blood, respiratory, urine, wound, cerebrospinal fluid, other body fluid, unknown type) obtained between 24 hours before sepsis onset and 1 hour after sepsis onset, and all Elixhauser comorbidities.

Abbreviations: ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.