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CHARACTERISTICS AND PREDICTORS OF PATIENTS WITH SEPSIS WHO ARE CANDIDATES FOR MINIMALLY INVASIVE APPROACH OUTSIDE OF INTENSIVE CARE UNIT

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ABSTRACT—**Objective:** To identify and describe characteristics of patients with sepsis who could be treated with minimally invasive sepsis (MIS) approach without intensive care unit (ICU) admission and to develop a prediction model to select candidates for MIS approach. **Methods:** A secondary analysis of the electronic database of patients with sepsis at Mayo Clinic, Rochester, MN. Candidates for the MIS approach were adults with septic shock and less than 48 hours of ICU stay, who did not require advanced respiratory support and were alive at hospital discharge. Comparison group consisted of septic shock patients with an ICU stay of more than 48 hours without advanced respiratory support at the time of ICU admission. **Results:** Of 1795 medical ICU admissions, 106 patients (6%) met MIS approach criteria. Predictive variables (age >65 years, oxygen flow >4 L/min, temperature <37°C, creatinine >1.6 mg/dL, lactate >3 mmol/L, white blood cells >15 $\times$ 10^9/L, heart rate >100 beats/min, and respiration rate >25 breaths/min) selected through logistic regression were translated into an 8-point score. Model discrimination yielded the area under the receiver operating characteristic curve of 79% and was well fitted (Hosmer-Lemeshow P = 0.94) and calibrated. The MIS score cutoff of 3 resulted in a model odds ratio of 0.15 (95% confidence interval, 0.08–0.28) and a negative predictive value of 91% (95% confidence interval, 88.69–92.92). **Conclusions:** This study identifies a subset of low-risk septic shock patients who can potentially be managed outside the ICU. Once validated in an independent, prospective sample our prediction model can be used to identify candidates for MIS approach.

KEYWORDS—Septic shock; vasopressor agent; central venous catheter; intensive care unit

INTRODUCTION

More than 5 million patients are admitted to the intensive care unit (ICU) in the United States each year (1). According to the American Hospital Association, the United States had 96,596 ICU beds, representing 16.7% of all hospital beds in 2018 (2). Three fourths of the U.S. hospitals (74%), with 94% of all ICU beds, are in metropolitan areas, with populations greater than 50,000, and only 1% of ICU beds are in rural areas with populations less than 10,000 persons (3). Over the past four decades, ICU beds have increased despite an overall decrease in hospital bed numbers in the United States (4,5). Similar trends have also been observed in other developed countries (6). Increased ICU beds and demand for critical care services are associated with the increasing geriatric population, improved life expectancy, and advanced therapeutics. However, despite the growing number of ICU beds, many countries, including the United States, struggled to meet the demand for critical care services necessitated by the COVID-19 pandemic (7,8)

Meeting the demand for critical services requires increasing the number of ICU beds. However, this is a costly solution as each additional ICU bed requires complex logistics to support it and a multidisciplinary ICU team. Using strategies for appropriate ICU patient selection is one method of increasing the availability of critical care beds to those patients requiring ICU-level care without incurring the direct and indirect costs otherwise associated with this feat.

Sepsis without the need for mechanical ventilation is among the top 5 ICU admission diagnoses (1). The number of patients with sepsis continues to rise in concordance with the incidence of septic shock, which has increased from 12.8 per 1,000 hospitalizations in 2005 to 18.6 in 2014 (9). In patients with septic shock, hypotension persists despite fluid resuscitation necessitating the initiation of intravenous (IV) vasopressor agents. Even a short course of vasopressors requires the placement of a central venous catheter (CVC) and monitoring in the ICU. Recently, studies have established the safety of short-term vasopressor use *via* peripheral IV catheter, thus avoiding the need for CVC placement (10). In addition, strategies such as accepting lower mean arterial pressure goals or off-label use of midodrine may decrease the duration of vasopressor treatment in patients at low risk of deterioration (11,12). The need for continuous monitoring while on vasopressors is the main indication for ICU admission for many patients treated in the ICU. However, there is a paucity of strategies to

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identify patients with sepsis, at low risk of deterioration, who require only short-term ICU level care (24–48 hours) and low-dose IV vasopressor support.

We suggest defining minimally invasive sepsis (MIS) approach as vasopressors administration *via* peripheral venous catheter and noninvasive monitoring in a subset of patients with septic shock who do not require advanced ICU interventions such as mechanical ventilation, cardioversion, continuous renal replacement, etc. Patients with sepsis who need procedures for source control (e.g., interventional radiology guided drainage, surgery, endoscopic procedures, etc.) could be candidates for MIS approach if source control has been achieved before consideration of ICU admission.

Our main objective was to identify and describe the subset of patients with septic shock who need short-term (<24 h) vasopressor support and no other interventions that would require ICU-level care. In addition, we aimed to develop a prediction model to identify candidates appropriate for minimally invasive sepsis approach without requiring admission to ICU.

MATERIALS AND METHOD

Study design

This study is a secondary analysis of a single-center, retrospective, institutional database of patients with sepsis. This study was approved by the Mayo Clinic institutional review board (IRB# 20-010541 titled "Identifying low-risk patients for minimally invasive sepsis management") on October 20, 2020, and was funded by Mayo Clinic Critical Care intramural research grant. All included patients or their legally authorized representatives provided a prior research authorization consenting to the use of their medical records for research purposes. The study was conducted per the ethical standards of the institutional committee on human experimentation and in accordance with the Helsinki Declaration.

Patient population

Study participants were identified from an established database of all index admissions of consecutive adult patients (age ≥18 years) to adult ICUs (medical ICU [MICU], coronary care unit, thoracic/vascular ICU, mixed medical/surgical ICU, cardio surgical ICU, and the neurocritical care ICU) at Mayo Clinic Hospital in Rochester, Minnesota, between January 1, 2009, and October 31, 2015. Details of the population and septic shock definition have been previously described (13). Briefly, septic shock was defined as patients with suspected infection, meeting two systemic inflammatory response syndrome criteria, and having persistent hypotension requiring vasopressors to keep mean arterial blood pressure ≥65 mm Hg and a serum lactate level >2 mmol/L despite adequate volume resuscitation (14,15).

This study included patients with septic shock who were admitted to the MICU directly from the emergency department (ED). Patients from surgical ICUs, MICU admissions from the general ward, admissions for postprocedural monitoring, and patients on invasive or noninvasive (continuous positive airway pressure, bilevel positive airway pressure, and oxygen inhalation *via* high-flow nasal cannula) respiratory support before ICU admission were excluded.

We identified candidates for minimally invasive sepsis approach based on the following criteria: patients with septic shock requiring <48 hours of ICU stay and <24 hours of IV vasopressor support. Furthermore, such patients must not have required invasive or noninvasive respiratory support or continuous renal replacement therapy and were alive at ICU and hospital discharge. The comparison group consisted of patients with septic shock who required more than 48 hours of ICU level care and did not need invasive or noninvasive respiratory support at ICU admission.

Data collection

Data for this study were collected from the original database from which our patient population was identified, United Data Platform (UDP), and supplemented by manual chart review. Data in the original database were abstracted using the Mayo Clinic ICU DataMart (13,16). The ICU DataMart is a Microsoft SQL-based warehouse capture tool that catalogs clinical data collected in real time. We have previously described and validated these data warehouses and extraction techniques as an institutional resource that contains real-time electronic medical record data from the ICU and acute care environments (16). We collected demographics, ICU admission and discharge times, use of invasive and noninvasive ventilation, Acute Physiology, Age, Chronic Health Evaluation III, and the Sequential Organ Failure Assessment scores using the ICU DataMart.

In this study, we focused on the lab values (serum lactate, serum creatinine, blood urea nitrogen, electrolytes, and white blood cells) and vital signs (respiratory rate, blood pressure, heart rate, and temperature) at the time of ICU admission. Data on laboratory values and vital signs were collected using the UDP, the clinical data repository for Mayo Clinic, and a manual chart review. Mayo Data Explorer (MDE) was used to access the data contained within the UDP. Mayo Data Explorer is an interface for UDP, which can look for patient information, including their demographics, flow sheets, laboratory data, clinical notes, etc. The data in MDE are obtained from multiple clinical and hospital source systems within Mayo Clinic and is supported by Mayo Clinic Information and technology department (17). Furthermore, the diagnosis of septic shock, use of vasopressors, vital signs, and laboratory values at the time of ICU admission were confirmed independently by two of the authors (AW, RS) to ensure the accuracy of diagnosis and vasopressor needs.

Statistical analysis

Data are summarized as median with interquartile range (IQR) when quantitative or count with associated percentages when qualitative. Wilcoxon rank test was used to compare continuous variables with skewed distribution. The chi-square test was used to compare categorical variables when the number of elements was ⩾ 5; otherwise, Fisher exact test was used. Minimally invasive sepsis prediction model was developed in the following steps. First, variables for the prediction model were selected using the least absolute shrinkage and selection operator (LASSO) regression method and were refined with clinical reasoning. Second, a multivariate logistic regression model was created using the selected continuous variables and the model's discrimination performance was assessed. Third, in conjunction with a prediction profiler (Classification and Regression Tree), the optimal cutoff point for each continuous variable was determined resulting in the categorization of each predictor variable. Fourth, using the categorical variables, odds ratios (ORs) were calculated *via* a multivariate logistic regression model, which in turn were used to assign points for each level of the categorical variable. Fifth, each patient's MIS score was calculated using the above derived points, and a univariate logistic regression model was created allowing for the derivation of pertinent coefficients, OR, and confidence intervals (CIs) were then derived. The discrimination of the resultant model was assessed using the area under the receiver operating characteristic curve (ROC: AUC). Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test and calibration with a plot of the predicted *versus* observed proportions for each point of the MIS score. A P value ≤ 0.05 was considered statistically significant. Data analysis was performed using JMP Statistical Software (Version 16.0.0; SAS Institute, Cary, NC) and R Statistical Software (R Version 4.1.2). R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

RESULTS

We identified 6,307 patients with septic shock from January 2009 to October 2015. After the application of our exclusion criteria from 1795 MICU admissions, we identified 106 patients (6%) who met our criteria for the minimally invasive sepsis approach (MIS group) and 262 patients in the comparison group (non-MIS group). Of 262, 109 patients were randomly selected for comparative analysis. After manual chart review, we had 106 in the MIS group and non-MIS group contained 97 unique patients (Fig. 1).

Baseline patient characteristics are summarized in Table 1. The MIS group was younger, had lower respiratory rate, lactate, creatinine, blood urea nitrogen levels, and white blood cell count, but higher temperature than the non-MIS group ($P < 0.05$ for all). More patients in the MIS group were started on vasopressors within 1 h of ED disposition. There was no statistically significant difference in sex, do not resuscitate and do not intubate status, systolic and diastolic blood pressure, heart rate, and source of infection among the two groups.

Predictive variables (with cutoff values) selected using clinical and statistical criteria described previously used to create the logistic model were age >65 years, oxygen flow >4 L/min, temperature <37°C, creatinine >1.6 mg/dL, lactate >3 mmol/L, white blood cells >15 × 10^9/L, heart rate >100 beats/min, and respiration rate >25 breaths/min. The estimates of the coefficients and P values for the variables in continuous and categorical forms are provided in Table 2 and Table 3, respectively. For variables in the continuous form, the ROC area under the curve was 79% (Supplementary Fig. 1, http://links.lww.com/SHK/B652) and 80% (Supplementary Fig. 2, http://links.lww.com/SHK/B652) for variables in categorical form. The corresponding points assigned to each variable based on OR and clinical reasoning are provided in Table 3. Using those points univariate logistic model was created with β of −0.865, standard error of 0.13, and $P \leq 0.00001$. Model discrimination yielded ROC area under the curve of 79% (95% CI = 73–85; Fig. 2). The Hosmer-Lemeshow goodness-of-fit test showed that observed event rates were well matched to the predicted event rates (chi-square = 2.95, P = 0.94). The model was well calibrated as depicted with a plot of the predicted *versus* observed proportions for each point of MIS score (Fig. 3).

Using an MIS score cutoff of 3 resulted in a predictive model OR of 0.15 (95% CI = 0.08–0.28) and a negative predictive value of 91% (using the observed prevalence of minimally invasive sepsis patients approximately 20%). Model performance is described in Table 4.

DISCUSSION

This is the first study to identify the characteristics and predictors of patients with sepsis whose only ICU need is short-term IV vasopressor infusion and who therefore could be candidates for minimally invasive approach without the need for admission to the ICU. Once externally validated, our prediction model with an AUC of 79% and negative predictive value of 91% could be used for triage decisions to minimize patient burden associated with ICU stay (central venous catheterization, noise, etc) and preserve valuable ICU beds at the time of national shortage.

The current model development is focused on patients with septic shock in the ED who would otherwise be treated in the MICU. Surgical patients were excluded as they often develop septic shock in the postoperative period and often require ICU interventions

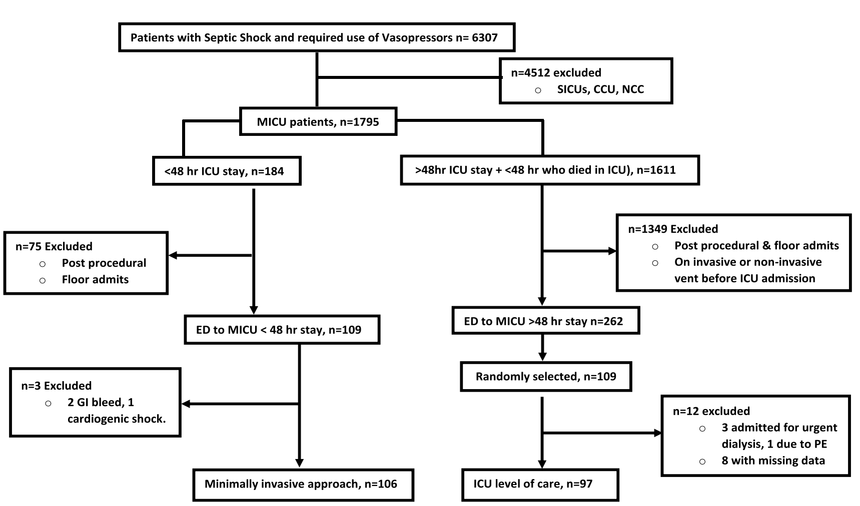

FIG. 1. **Flow chart of inclusion and exclusion criteria**. CCU, coronary care unit; ICU, intensive care unit; MICU, medical intensive care unit; NCC, neuro critical care; SICUs, surgical intensive care units.

TABLE 1. **Baseline characteristics**

Characteristic*	Minimally invasive Sepsis (n = 106)	Not minimally invasive sepsis (n = 97)	*P*
Age, median (IQR), y	65.3 (56.3–75.7)	73.0 (57.9–80.2)	0.02
Female, n (%)	56 (52.8)	46 (47.4)	0.48
DNR/DNI, n (%)	21 (19.8)	26 (26.8)	0.25
Lactate, mmol/L	2.0 (1.3–2.7)	2.7 (2.0–4.1)	<0.0001
Oxygen flow, L/min	3.0 (2.0–4.0)	3.0 (2–4.2)	0.02
Creatinine, mg/dL	1.3 (1.0–2.0)	1.9 (1.3–3.4)	<0.0001
Blood urea nitrogen, mg/dL	28.0 (15.0–40.0)	41.0 (28.0–67.5)	<0.0001
Vasopressor use within first hour of admission, n (%)	43 (40.6)	22 (22.7)	0.007
Systolic blood pressure, mm Hg	97.0 (88.0–108.0)	97.0 (89.0–109.5)	0.74
Mean arterial pressure, mm Hg	66.0 (58.0–75.0)	66.0 (59.0–76.0)	0.74
Heart rate, beats/min	97.0 (83.0–112.3)	99.0 (80.0–113.5)	0.88
Respiratory rate, breaths/min	21.0 (17.0–24.3)	23.0 (19.0–27.0)	0.01
Temperature, °C	37.1 (36.9–38.0)	37.0 (36.5–37.7)	0.02
Serum bicarbonate, mmol/L	20.0 (17.0–22.0)	20.0 (16.0–24.0)	0.36
Serum sodium, mmol/L	136.0 (133.0–139.0)	135.0 (131.5–140.0)	0.47
Hemoglobin, g/dL	10.4 (9.0–12.0)	11.2 (9.3–12.7)	0.06
Platelets, 10^9/L	187.5 (116.0–249.3)	167.0 (114.0–229.0)	0.41
White blood cells, 10^9/L	12.1 (7.7–14.9)	14.9 (9.0–18.6)	0.003
CVC placed, n (%)	83 (78)	N/A	N/A
APACHE III (24 hours)	65.5 (52.8–76.0)	84.0 (72.5–98.0)	<0.0001
SOFA day 1	6.0 (5.0–8.0)	9.0 (6.5–11.0)	<0.0001
Positive culture (72 h prior through ICU stay), n (%)	7 (6.6)	15 (15.5)	0.07
Source of infection			
Biliary	5 (4.7)	5 (5.2)	0.17
Central nervous system	0 (0)	2 (2.1)	
Non biliary intraabdominal	4 (3.8)	10 (10.3)	
Musculoskeletal	5 (4.7)	3 (3.1)	
Pulmonary	19 (17.9)	26 (26.8)	
Skin and soft tissue	8 (7.6)	6 (6.2)	
Urinary tract	25 (23.6)	23 (23.7)	
>1 source	2 (1.9)	1 (1.0)	
Unknown source	38 (35.9)	21 (21.7)	

*All vital sign values and laboratory values are at the time of ICU admission.
DNI, do not intubate; DNR, do not resuscitate; N/A, not available.

beyond short-term vasopressor use. Patients who died during hospitalization were also excluded from the MIS group considering that they were very sick for management outside the ICU.

The standard approach to treatment of septic shock, regardless of the etiology or degree of end-organ failure, is ICU admission for hemodynamic support *via* vasopressor administration and continuous monitoring. This treatment approach has become algorithmic and the decision to implement this is often made without consideration of whether CVC placement and continuous monitoring are truly necessary. Placement of CVC is burdensome for patients, time-consuming, and requires expertise and resources, which can delay the initiation of vasopressors and increase mortality (18,19). In addition, CVC-related serious complications, including mechanical, infectious, and thromboembolic, occur in more than 15% of patients (20).

Recent studies have demonstrated the safety and efficacy of early initiation of vasopressors *via* peripheral venous catheters with close monitoring of the patients (10,20,21). In a recent systematic review on the safety of peripheral vasopressor administration, no episodes of tissue necrosis or limb ischemia were reported, extravasation was uncommon (3.4% [95% CI = 2.5–4.7]), and all extravasation events required only conservative management. The mean duration of vasopressor use in this study was 22 h (95% CI = 8–36 h) (10). Similar findings were reported in a meta-analysis by Tran et al. and demonstrated in a pilot study by Groetzinger et al. (22,23). The frequency of complications associated with vasopressor administration *via* peripheral catheters could be further reduced using ultrasound guidance, wide-bore cannulas, and midline

TABLE 2. **Multivariate analysis of predictive variables in the continuous form**

Predictors*	OR	95% CI	*P*
Oxygen flow, L/min	0.79	0.68–0.93	0.0008
Creatinine	0.69	0.52–0.90	0.003
Age	0.98	0.96–1.00	0.03
Temperature	1.45	1.02–2.05	0.03
Lactate	0.77	0.61–0.97	0.02
White blood cells	0.97	0.93–1.01	0.16
Heart rate	1.00	0.98–1.02	0.88
Respiratory rate	0.79	0.87–1.00	0.04

*Continuous variables selected through regression method and clinical reasoning to generate MIS score.

TABLE 3. **Predictive model for minimally invasive sepsis approach**

Predictor	OR	95% CI	*P*	Points
Oxygen flow >4 L/min	0.24	0.10–0.60	0.002	1.5
Creatinine >1.6	0.31	0.16–0.60	0.0004	1.5
Age >65	0.44	0.22–0.89	0.02	1
Temperature < 37	0.33	0.17–0.66	0.001	1
Lactate >3	0.50	0.24–1.03	0.06	1
WBC > 15	0.35	0.17–0.70	0.003	1
Heart rate > 100	0.56	0.28–1.15	0.11	0.5
Respiratory rate > 25	0.65	0.29–1.45	0.29	0.5

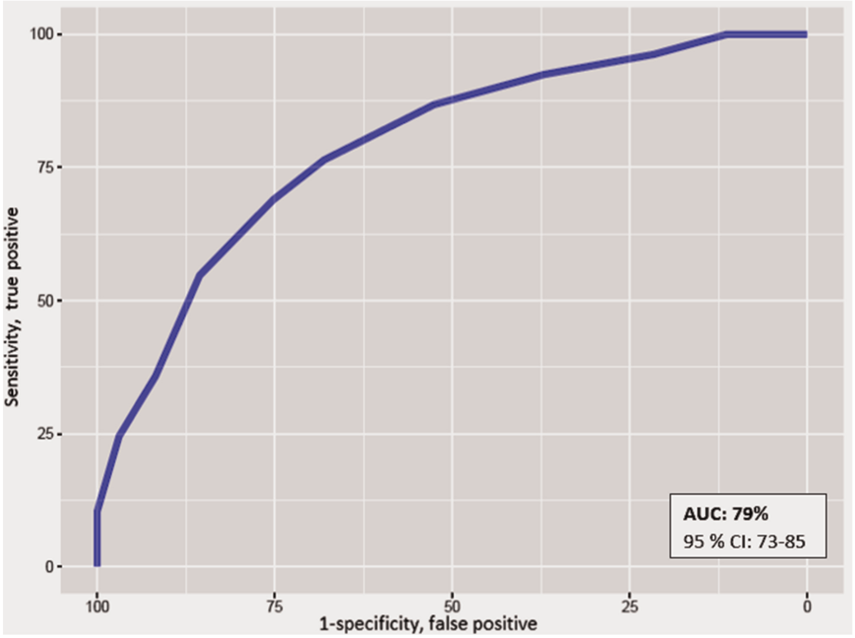

FIG. 2. **Receiver operating characteristic curve for predicting candidates for minimally invasive approach**.

catheters (23,24). In our study, the MIS group was admitted to ICU for a short duration of vasopressor administration and monitoring that could have been safely performed in an alternative setting using peripheral administration of vasopressors, as described above.

Midodrine has been shown to reduce the duration and cumulative dose of vasopressors and improve lactic acid clearance in patients with sepsis when used during early hours (12,25). It is possible that midodrine could be used in certain MIS group patients precluding the need for vasopressor support. We anticipate that further studies will provide evidence of the appropriateness of midodrine use in the MIS approach.

Some experts suggest that ICU beds are not adequately used and that many patients admitted to ICU are either too healthy or

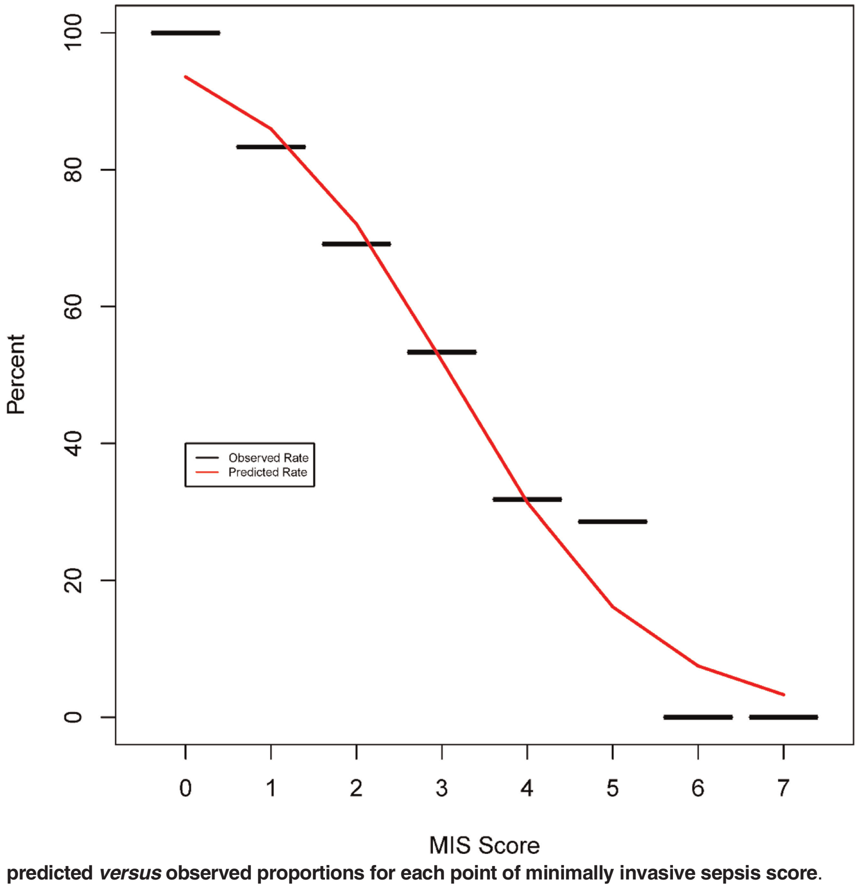

FIG. 3. **Model calibration: predicted *versus* observed proportions for each point of minimally invasive sepsis score**.

TABLE 4. **Performance of minimally invasive sepsis approach score**

Statistic	Value	95% CI
Sensitivity	68.87%	59.14%–77.51%
Specificity	75.26%	65.46%–83.46%
Positive likelihood ratio	2.78	1.92–4.03
Negative likelihood ratio	0.41	0.30–0.56
Positive predictive value*	41.03%	32.46%–50.18%
Negative predictive value*	90.63%	87.69%–92.92%
Accuracy*	73.98%	67.37%–79.87%
Disease prevalence	20.00%	—

*These values are dependent on disease prevalence.

at the end of life and do not benefit from critical care services (1,26). Unnecessary ICU admissions carry a significant financial burden, risk of iatrogenic harm, and can be frightening experiences for the patients (27,28). Appropriate use of ICU beds is crucial to the preservation of resources for those who benefit the most. Our study suggests early identification of a group of low-risk patients to prevent unnecessary ICU admissions while still allowing for appropriate management *via* the MIS approach.

The strengths of the study include well-defined criteria and use of routinely collected electronic health record data that are readily available at the time of ED disposition, which facilitated model programming. The limitations of our study include the single-center cohort of predominantly White patients. Thus, our results may not generalize to other settings. The preeminent limitation is the absence of independent prospective validation of our model. In addition, a retrospective electronic health record database does not capture ancillary information or clinical decision making regarding the need for ICU admission beyond IV vasopressors. Certain nontangible care components are easily accessible in the ICU environment as compared with the general ward. Practice variability, resource availability, and nursing oversight are some other components that need to be studied, which were not part of this article. Furthermore, because of limitations inherent to the UDP and the means by which data were collected, we could not reliably calculate the rate and cumulative dose of vasopressors administered to each patient.

After prospective validation, we plan to implement our model at the institutional level in collaboration with the emergency, hospital, and critical care medicine departments for resource utilization and triaging of precious ICU beds to reduce strain on the intensive care services. We have done this for other interventions (29). We plan to use human filter (“control tower operator”) to increase accuracy and minimize clinicians’ burden

CONCLUSIONS

Our study identified patients with sepsis at low risk of deterioration with an expected short duration of vasopressors and no need for other ICU interventions, the MIS group. Once validated in an independent, prospective sample, our prediction model can be used to identify candidates for minimally invasive sepsis approach outside of the traditional ICU setting.

REFERENCES

1. Society of Critical Care Medicine. Critical care statistics. Available at: https://www.sccm.org/Communications/Critical-Care-Statistics. Accessed May 22, 2022.
2. American Hospital Association. Fast facts on U.S. hospitals. 2020. Available at: https://www.aha.org/statistics/fast-facts-us-hospitals. Published 2018, March 18. Accessed June 15, 2022.
3. Society of Critical Care Medicine. United States resource availability for COVID-19. Available at: https://www.sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19. Published 2020, March 3. Accessed May 22, 2022.
4. Halpern NA, Tan KS, DeWitt M, et al. Intensivists in U.S. acute care hospitals. *Crit Care Med*. 2019;47(4):517–525.
5. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med*. 2008;36(10):2787–2793, e2781-2789.
6. Thattil R, Klepzig D, Schuster M. Intensive care capacities in Germany: provision and usage between 1991 and 2009 [in German]. *Anaesthesist*. 2012;61(1):56–62.
7. Domecq JP, Lal A, Sheldrick CR, et al. Outcomes of patients with coronavirus disease 2019 receiving organ support therapies: the international viral infection and respiratory illness universal study registry. *Crit Care Med*. 2021;49(3):437–448.
8. Johnson SW, Garcia MA, Sisson EK, et al. Hospital variation in management and outcomes of acute respiratory distress syndrome due to COVID-19. *Crit Care Explor*. 2022;10(2):e0638.
9. Kadri SS, Rhee C, Strich JR, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. *Chest*. 2017;151(2):278–285.
10. Tian DH, Smyth C, Keijzers G, et al. Safety of peripheral administration of vasopressor medications: a systematic review. *Emerg Med Australas*. 2020;32(2):220–227.
11. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. *JAMA*. 2020;323(10):938–949.
12. Rizvi MS, Trivedi V, Nasim F, et al. Trends in use of midodrine in the ICU: a single-center retrospective case series. *Crit Care Med*. 2018;46(7):e628–e633.
13. Kashyap R, Singh TD, Rayes H, et al. Association of septic shock definitions and standardized mortality ratio in a contemporary cohort of critically ill patients. *J Crit Care*. 2019;50:269–274.
14. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644–1655.
15. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
16. Herasevich V, Kor DJ, Li M, et al. ICU data mart: a non-iT approach. A team of clinicians, researchers and informatics personnel at the Mayo Clinic have taken a homegrown approach to building an ICU data mart. *Healthc Inform*. 2011;28(11):42, 44–45.
17. Mayo Data Exploere. Mayo Clinic Foundation United Data Platform. Available at: https://itconnect.mayo.edu/mayo-data-explorer. Accessed 2022.
18. Bai X, Yu W, Ji W, et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care*. 2014;18(5):532.
19. Beck V, Chateau D, Bryson GL, et al. Timing of vasopressor initiation and mortality in septic shock: a cohort study. *Crit Care*. 2014;18(3):R97.
20. Stolz A, Efendy R, Apte Y, et al. Safety and efficacy of peripheral versus centrally administered vasopressor infusion: a single-centre retrospective observational study. *Aust Crit Care*. 2021;35:506–511.
21. Delaney A, Finnis M, Bellomo R, et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: a retrospective cohort study. *Emerg Med Australas*. 2020;32(2):210–219.
22. Groetzinger LM, Williams J, Svec S, et al. Peripherally infused norepinephrine to avoid central venous catheter placement in a medical intensive care unit: a pilot study. *Ann Pharmacother*. 2022;56(7):773–781.
23. Tran QK, Mester G, Bzhilyanskaya V, et al. Complication of vasopressor infusion through peripheral venous catheter: a systematic review and meta-analysis. *Am J Emerg Med*. 2020;38(11):2434–2443.
24. Prasanna N, Yamane D, Haridasa N, et al. Safety and efficacy of vasopressor administration through midline catheters. *J Crit Care*. 2021;61:1–4.
25. Lal A, Trivedi V, Rizvi MS, et al. Oral midodrine administration during the first 24 hours of sepsis to reduce the need of vasoactive agents: placebo-controlled feasibility clinical trial. *Crit Care Explor*. 2021;3(5):e0382.
26. Rigaud JP, Giabicani M, Beuzelin M, et al. Ethical aspects of admission or non-admission to the intensive care unit. *Ann Transl Med*. 2017;5(suppl 4):S38.
27. Agrawal A, Gandhe MB, Gandhe S, et al. Study of length of stay and average cost of treatment in medicine intensive care unit at tertiary care center. *J Health Res Rev*. 2017;4(1):24.
28. Paoli CJ, Reynolds MA, Sinha M, et al. Epidemiology and costs of sepsis in the United States—an analysis based on timing of diagnosis and severity level. *Crit Care Med*. 2018;46(12):1889–1897.
29. Wilson PM, Philpot LM, Ramar P, et al. Improving time to palliative care review with predictive modeling in an inpatient adult population: study protocol for a stepped-wedge, pragmatic randomized controlled trial. *Trials*. 2021;22(1):635.