

An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU

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Objectives: Sepsis is among the leading causes of morbidity, mortality, and cost overruns in critically ill patients. Early intervention with antibiotics improves survival in septic patients. However, no clinically validated system exists for real-time prediction of sepsis onset. We aimed to develop and validate an Artificial Intelligence Sepsis Expert algorithm for early prediction of sepsis.

Design: Observational cohort study.

Setting: Academic medical center from January 2013 to December 2015.

Patients: Over 31,000 admissions to the ICUs at two Emory University hospitals (development cohort), in addition to over 52,000 ICU patients from the publicly available Medical Information Mart for Intensive Care-III ICU database (validation cohort). Patients who met the Third International Consensus Definitions for Sepsis (Sepsis-3) prior to or within 4 hours of their ICU admission were excluded, resulting in roughly 27,000 and 42,000 patients within our development and validation cohorts, respectively.

Interventions: None.

Measurements and Main Results: High-resolution vital signs time series and electronic medical record data were extracted. A set of 65 features (variables) were calculated on hourly basis and passed to the Artificial Intelligence Sepsis Expert algorithm to predict onset of sepsis in the proceeding T hours (where $T = 12, 8, 6$, or 4). Artificial Intelligence Sepsis Expert was used to predict onset of sepsis in the proceeding T hours and to produce a list of the most significant contributing factors. For the 12-, 8-, 6-, and 4-hour ahead prediction of sepsis, Artificial Intelligence Sepsis Expert achieved area under the receiver operating characteristic in the range of 0.83–0.85. Performance of the Artificial Intelligence Sepsis Expert on the development and validation cohorts was indistinguishable.

Conclusions: Using data available in the ICU in real-time, Artificial Intelligence Sepsis Expert can accurately predict the onset of sepsis in an ICU patient 4–12 hours prior to clinical recognition. A prospective study is necessary to determine the clinical utility of the proposed sepsis prediction model. (*Crit Care Med* 2018; 46:547–553)

Key Words: informatics; machine learning; organ failure; prognostication; sepsis

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Sepsis, a dysregulated immune-mediated host response to infection, is prevalent, lethal, and costly (1–4). Recent literature suggests that early and appropriate antibiotic therapy is the main factor predicting sepsis outcomes (5). Identifying those at risk for sepsis and initiating appropriate treatment, prior to any clinical manifestations, would have a significant impact on the overall mortality and cost burden of sepsis.

Clinical decision support (CDS) tools can help identify those at highest risk for future sepsis. Existing work on electronic medical record (EMR) and laboratory data seem promising (6–8), but

they are limited by being static, or collected at low or inconsistent frequencies. The dynamics of heart rate (HR) and blood pressure (BP) extracted directly from the electrocardiogram and arterial waveform can improve mortality prediction over clinical data (demographics or data collected at low frequency) in ICU patients with transient hypotension (9). The objective of this study is to demonstrate that a high-performance prediction model can be derived from a combination of EMR and high-frequency physiologic data (collected at least once per second). We further test the relationship between the prediction lead time (prediction window) and predictive accuracy of the model and investigate questions of generalizability and interpretability of the proposed model.

METHODS

Study Population and Data Sources

All ICU patients 18 years old or older were included from two hospitals within the Emory Healthcare system, as well as an external publicly available ICU database (10). This investigation was conducted according to Emory University Institutional Review Board approved protocol 33,069. Patients were followed throughout their ICU stay until discharge or development of sepsis, according to the Third International Consensus Definitions for Sepsis (Sepsis-3). Specifically, all episodes of suspected infection ($t_{\text{suspicion}}$) were identified as the earlier timestamp of antibiotics and blood cultures within a specific time span; if the antibiotic was given first, the culture sampling must have been obtained within 24 hours. If the culture sampling was first, the antibiotic must have been ordered within 72 hours. The onset time of sepsis (t_{sepsis}) was then defined as an episode of suspected infection with two or more points change in the Sequential Organ Failure Assessment (SOFA) score (t_{SOFA}) from up to 24 hours before to up to 12 hours after the $t_{\text{suspicion}}$ ($t_{\text{SOFA}} + 24\text{ hr} > t_{\text{suspicion}} > t_{\text{SOFA}} - 12\text{ hr}$). These definitions were based on a recent assessment of the revised clinical criteria for sepsis (11). Finally, we defined t_{onset} as the minimum of t_{sepsis} and t_{SOFA} . Though our primary outcome was t_{sepsis} , we report the predictive performance of our algorithm also on t_{SOFA} and t_{onset} for completeness and to facilitate comparison with the existing literature.

Data from the EMR (Cerner, Kansas City, MO) were extracted through a clinical data warehouse (MicroStrategy, Tysons Corner, VA). High-resolution HR and BP time series at 2 seconds resolution were collected from select ICUs, through the BedMaster system (Excel Medical Electronics, Jupiter, FL), which is a third party software connected to the hospital's General Electric monitors for the purpose of electronic data extraction and storage of high-resolution waveforms. Patients were excluded if they developed sepsis within the first 4 hours of ICU admission (by analyzing pre-ICU IV antibiotic administration and culture acquisition) or if their length of ICU stay was less than 8 hours or more than 20 days.

Feature Extraction and Machine Learning

A total of 65 features from the EMR and high-resolution bedside monitoring data. These features were used as inputs

to a modified Weibull-Cox proportional hazards model, the machine learning algorithm used in this study. See **Appendices B and C** (Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>) for further details on feature extraction and machine learning and **Appendix F** (Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>) for a glossary of machine learning-related terms and their meanings.

Statistical Methods

For all continuous variables, we report medians ([25–75th percentile]) and use a two-sided Wilcoxon rank-sum test when comparing two populations. For binary variables, we report percentages and use a two-sided chi-square test to assess differences in proportions between two populations. Artificial Intelligence Sepsis Expert (AISE) classification results for T hours ($T = 12, 8, 6$ or 4 hr) ahead predictions are based on a random split into 80% training and 20% testing, and the area under receiver operating characteristic (AUROC) curves statistics for both the training and the testing sets are reported, as well as specificity (1-false alarm rate) and accuracy at a fixed 85% sensitivity level.

RESULTS

Our development cohort included a total of 27,527 patients, 2,375 (8.6%) of whom developed sepsis in the ICU with a median lag time of 23.9 hours (**Appendix – Table A1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>). Those who developed sepsis tended to have a slightly higher percentage of male patients (56.2% vs 52.4%) and have more comorbidities (Charlson Comorbidity Index [CCI] 4 vs 2). Septic patients had longer median lengths of ICU stay (5.9 vs 1.9 d), higher median SOFA scores (5.0 vs 1.7), and higher hospital mortality (14.5% vs 2.9%). Similar patterns were observed within our validation cohort (**Appendix – Table E1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>).

Both training set and testing set AUROCs for detecting sepsis were 0.79 or higher for every prediction task (t_{sepsis} , t_{SOFA} , t_{onset}) and prediction window ($n = 4, 6, 8$, and 12 hr) (**Fig. 1**). The best performance was achieved for predicting t_{SOFA} 4 hours in advance (AUROC of 0.87), which was slightly higher than predicting t_{sepsis} 4 hours in advance (AUROC of 0.85). In our development cohort, roughly 21% of the time t_{SOFA} occurred after t_{sepsis} (**Appendix D**, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>). We therefore defined t_{onset} as the earliest timestamp of the two (t_{sepsis} and t_{SOFA}), which proved more difficult to predict (4 hr prediction AUROC of 0.82). When sensitivity was fixed at 85% (risk score = 0.45), specificity in the test cohort was highest for T_{SOFA} prediction (72%), followed by t_{sepsis} (67%), and the lowest for t_{onset} (64%) (**Table 1**).

Model performance decreased slightly when prediction occurred over longer time windows regardless of the sepsis time-point of interest (**Figure 2** & **Table 1**). To predict t_{sepsis} , model AUROC decreased from 0.85 at a 4-hour prediction window to 0.83 at a 12-hour window. Specificity demonstrated similar declines when sensitivity was fixed at 85% (67% with

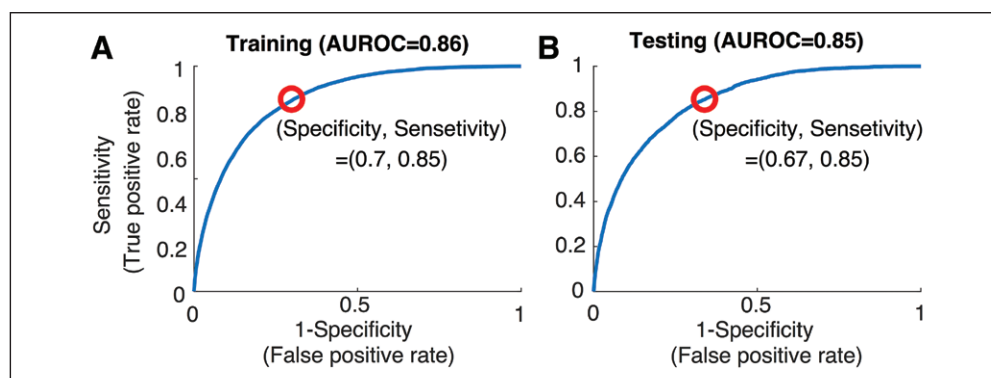


Figure 1. Area under the receiver operating characteristic (AUROC) curves for predicting t_{sepsis} 4 hr in advance. Catching 85% of the septic patients yielded 30% false alarms (specificity = 0.70) within the training set (**A**) and 33% false alarms (specificity = 0.67) within the testing set (**B**). See Table 2 for information on the false alarms.

4-hr windows vs 63% at 12-hr window). These findings were consistent across our development and validation cohorts (**Appendix, Fig. E1** and **Table E2**, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>).

Hospital mortality increased as the risk score for sepsis (t_{sepsis}) increased from 0 to 1 (**Table 2**). Those with a risk score of 0–0.2 had a mortality of 0.5%, whereas those with risk scores of greater than 0.8 had a 32.9% mortality rate. This was true even among those who were false positives, defined as those who did not develop sepsis in the predicted window but had risk scores of 0.45 or greater. In fact, the mortality was higher among false positives assigned the risk score of greater than 0.8, compared with those given a similar score in the total cohort (56.3% vs 32.9%). Compared with those who were false negatives, patients who were false positives had higher SOFA scores (4.0 [interquartile range (IQR), 2.0–7.0] vs 3.0 [IQR, 1.0–5.0]; $p < 0.01$), higher CCIs (4.0 [IQR, 2.0–6.0] vs 3.0 [IQR, 2.0–5.0]; $p < 0.01$), and higher hospital mortality (15.5% vs 6.4%; $p < 0.01$).

infection (as marked by t_{sepsis} ; AUROC 0.85), or the earlier of the two (namely, t_{onset} ; AUROC 0.82). Prediction performance is inversely proportional to size of the prediction window; AUROC, specificity, and accuracy for t_{sepsis} all decreased slightly as the prediction window lengthened from 4 to 12 hours but still provided high-performing models (AUROC of at least 0.83). We externally validated all findings in patients from a separate academic center.

As ICU clinicians are inundated with ever-increasing data collected at higher frequencies, machine learning will become more essential to research and clinical practice. Machine learning refers to a body of methods based on computer science that use patterns in data to identify or predict an outcome. Machine learning provides a powerful set of tools for describing relationships between features and the outcome(s) of interest (e.g., sepsis), particularly when they are nonlinear and complex. It is best used when there are a large number of variables, and overfitting (poor generalizability) can be a problem for traditional statistical methods.

DISCUSSION

In this study, we demonstrated that a high-performing prediction model (AUROC 0.85) can predict sepsis (t_{sepsis}) 4 hours in advance using EMR data combined with high-resolution time series dynamics of HR and BP. This is true no matter the outcome of interest, whether the prediction task involves more objective physiologic manifestations of sepsis (as captured by t_{SOFA} ; AUROC 0.87), clinical suspicion of

TABLE 1. Summary of Algorithm Performance on the Emory Cohort

| Performance Metric | 4 hr | 6 hr | 8 hr | 12 hr |
|---|-------------|-------------|-------------|-------------|
| t_{sepsis} Prediction testing set (training set) | | | | |
| AUROC | 0.85 (0.86) | 0.85 (0.85) | 0.84 (0.84) | 0.83 (0.83) |
| Specificity ^a | 0.67 (0.70) | 0.67 (0.68) | 0.65 (0.66) | 0.63 (0.65) |
| Accuracy | 0.67 (0.70) | 0.67 (0.68) | 0.66 (0.67) | 0.63 (0.65) |
| t_{SOFA} Prediction testing set (training set) | | | | |
| AUROC | 0.87 (0.88) | 0.85 (0.87) | 0.85 (0.86) | 0.82 (0.84) |
| Specificity ^a | 0.72 (0.74) | 0.67 (0.70) | 0.65 (0.68) | 0.59 (0.64) |
| Accuracy | 0.72 (0.74) | 0.68 (0.71) | 0.66 (0.68) | 0.60 (0.64) |
| t_{onset} Prediction testing set (training set) | | | | |
| AUROC | 0.82 (0.83) | 0.81 (0.82) | 0.80 (0.81) | 0.79 (0.80) |
| Specificity ^a | 0.64 (0.64) | 0.62 (0.62) | 0.58 (0.61) | 0.56 (0.58) |
| Accuracy | 0.64 (0.64) | 0.62 (0.62) | 0.58 (0.61) | 0.56 (0.59) |

AUROC = area under the receiver operating characteristic.

^aSensitivity was fixed at 0.85 (catching 85% of sepsis cases).

TABLE 2. Relationship Between Probability of Sepsis and Mortality for the Entire Cohort, Among the False-Positive Cases and the False-Negative Cases

| p of $t_{\text{sepsis}} < 4$ hr | $0 < p \leq 0.2$ | $0.2 < p \leq 0.4$ | $0.4 < p \leq 0.6$ | $0.6 < p \leq 0.8$ | $0.8 < p \leq 1.0$ |
|-----------------------------------|------------------|--------------------|--------------------|--------------------|--------------------|
| Overall cohort | | | | | |
| Expired (%) | 0.5 | 2.8 | 8.6 | 17.3 | 32.9 |
| Inpatient hospice (%) | 0.9 | 4.2 | 10.6 | 16.2 | 16.7 |
| False positives | | | | | |
| Expired (%) | — | — | 8.3 | 20.1 | 56.3 |
| Inpatient hospice (%) | — | — | 10.7 | 19.5 | 23.4 |
| False negatives | | | | | |
| Expired (%) | 5.7 | 7.3 | 1.7 | — | — |
| Inpatient hospice (%) | 2.9 | 8.2 | 11.7 | — | — |

Dashes indicate false positive can only happen for values greater than the detection threshold. Similarly, false negatives can only happen for values less than the detection threshold.

We had access to over 65 features in our analysis; we therefore used a modified regularized Weibull-Cox analysis, a type of machine learning approach that results in a more interpretable and generalizable survival model, to predict sepsis in ICU patients (See **Figure 3** for an example, and Appendix C for more details on this approach, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>).

Machine learning-based CDS tools embedded within EMR improve early detection and prompt treatment in those with early sepsis and can predict septic shock (12–15). EMR alerts to detect existing sepsis can improve adherence to treatment protocols, decreases time until antibiotic administration and length of hospital stay, and can improve mortality (16–18). They can predict septic shock with 85% accuracy using either EMR data or high-

resolution vital sign streams (12, 15). Still, a patient for whom CDS is used for septic shock prediction already has sepsis. Fluid and hemodynamic management would be the only modifiable intervention to provide those at risk for septic shock, but a recent study suggested that this is not associated with lower in-hospital mortality (5).

This study makes several significant contributions to the existing literature on sepsis prediction. The data used in our model are widely available in current practice. Lukaszewski et al (6) demonstrated that a neural network using only cytokine data predicted sepsis better than a similar algorithm using clinical EMR data. However, cytokines are not routinely measured, making it an impractical tool for contemporary practice. Wang et al (7) used simple EMR features such as WBC count, HR, and Acute Physiology and Chronic Health Evaluation 2 score and created

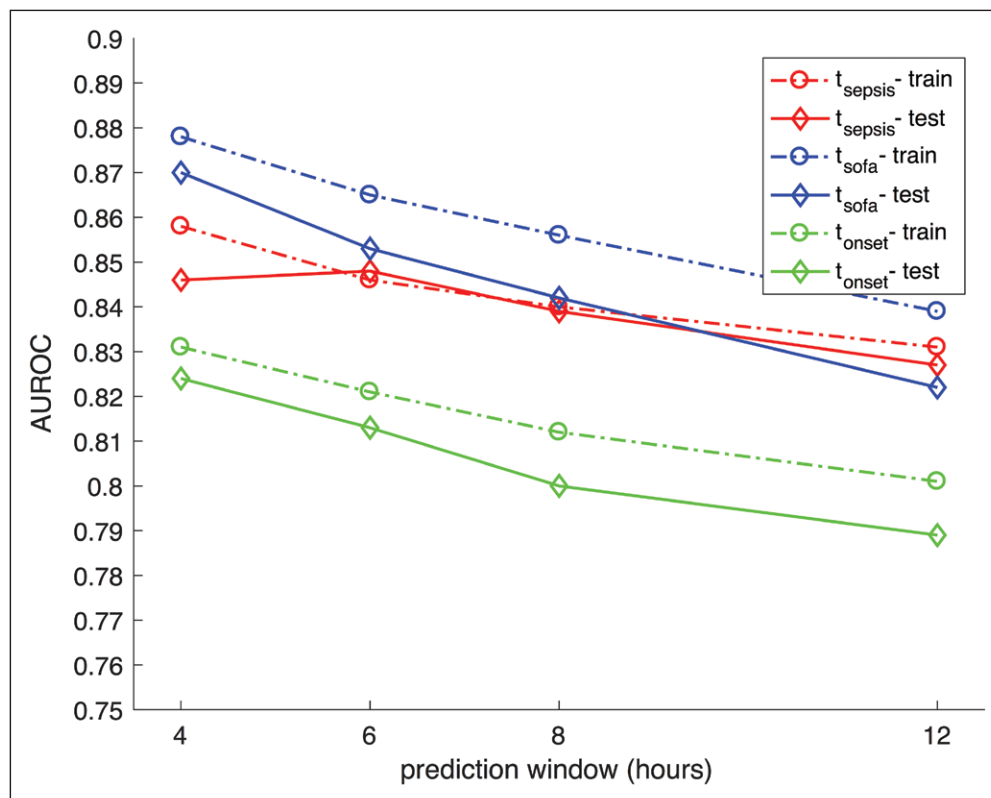


Figure 2. Summary of training (train) set (dashed lines) and testing set (solid lines) prediction performance of Artificial Intelligence Sepsis Expert on the Emory cohort. Area under the receiver operating characteristic (AUROC) curve as a function of prediction window shows a decreasing pattern. Across all windows, the best performance is achieved for predicting t_{sofa} , followed by t_{sepsis} , and finally t_{onset} . A close agreement between the train set and testing set performance indicates good generalizability.

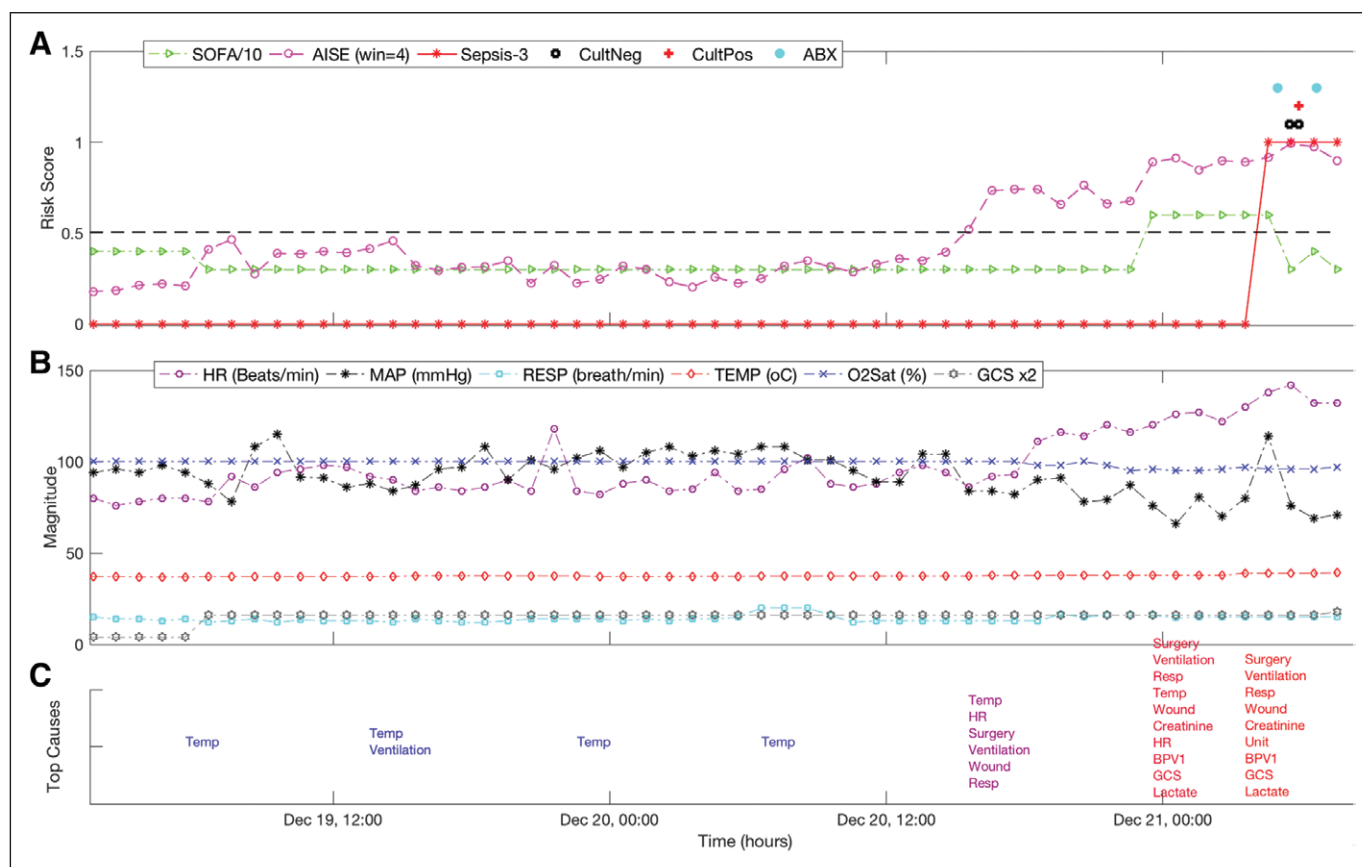


Figure 3. An illustrative example of the prediction performance of Artificial Intelligence Sepsis Expert (AISE). Hourly calculated Sequential Organ Failure Assessment (SOFA) score, Third International Consensus Definitions for Sepsis (Sepsis-3), and the AISE score are shown for one patient in **A**. Superimposed on the figure is the order time of three blood cultures and the administration time of two antibiotics. In **B**, commonly recorded hourly vital signs of the patient, including heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RESP), temperature (TEMP), oxygen saturation (O₂Sat), and the Glasgow Coma Score (GCS) are shown. **C**, the most significant features contributing to the AISE score (for clarity of presentation, only selected time points are shown). Notably, around 4 PM on December 20, roughly 8 hr prior to any change in the SOFA score, the AISE score starts to increase. The top contributing factors were slight changes in HR, RESP, and TEMP, given that the patient had surgery in the past 12 hr with a contaminated wound and was on a mechanical ventilator. Close to midnight on December 21, other factors such as multiscale entropy of MAP time series (BPV1), GCS, and Lactate show abnormal changes. Five hours later, the patient met the Sepsis-3 definition of sepsis. ABX = antibiotics, BPV1 = blood pressure variability (based on "multiscale entropy of MAP time series"), CultNeg = negative culture, CultPos = positive culture.

an estimate of future sepsis severity in ICU patients (scale of 0–1). Although their model was very good at classifying severe sepsis (by Sepsis-1 definition [19]) and its severity (AUROC 0.94), it averaged repeated measures for each feature during the first 24 hours of ICU stay. This is less useful for real-time use, and one cannot identify specific prediction windows in which sepsis would occur since time series inputs are not used.

Our algorithm is among the first to predict sepsis by combining data collected at different resolutions (low-resolution EMR data and high-resolution BPs and HRs). Others have used low-resolution inputs primarily, either as a single input feature by averaging repeated measures (7) or by retaining time series integrity (8). Coupling low-resolution with high-resolution data provide complementary information used by our algorithm to predict sepsis risk in our cohort. Two high-resolution features, entropy of HR, and BP, were important in model development. Multiscale entropy, one of many variability metrics thought to represent neurocardiac organ interaction (i.e., adjustments in autonomic tone), improves hospital mortality prediction in those with sepsis (20). The AISE system

can accommodate more input features as the medical community learns more about sepsis. As our biological and physiologic understanding of sepsis improves and new biomarkers are created, it may also allow clinicians to use the algorithm in smarter ways. Since AISE can inform the physician of the most relevant features contributing to the risk score over time (Appendix C, Visualization and Interpretability, Supplemental Digital Content 1, <http://links.lww.com/CCM/D147>), one can use what is known about sepsis and apply it to the clinical context to decide if and when one should act upon the prediction.

To our knowledge, this is the first study to demonstrate acceptable performance of a sepsis prediction algorithm over incrementally longer time windows. Desautels et al (8) used a proprietary machine learning algorithm with vital signs, pulse oximetry, GCS, and age as features and demonstrated moderate capability to predict sepsis 4 hours before it occurred (AUROC 0.74). Sepsis was defined as the first time at which there was a two-point increase in SOFA that preceded evidence of suspicion of infection. Our algorithm was superior to this using a similar sepsis definition (t_{SOFA}) over the same time

window (AUROC 0.87) and stayed superior up to a prediction window of 12 hours. The robustness of our model could at least be partly explained by the rich information provided by the different resolutions of our inputs.

Defining the onset of sepsis can be very subjective and provider dependent; we therefore assessed the performance of a range of clinically meaningful outcomes. The t_{SOFA} is the most objective of all three markers used and the easiest to predict using EMR and vitals data. In our datasets, roughly 20% of the time t_{SOFA} occurred after t_{sepsis} . We therefore introduced the t_{onset} as the minimum of t_{SOFA} and t_{sepsis} . However, t_{onset} was the most difficult to predict and had the lowest AUROC. This is not surprising, since prompt prediction of sepsis requires up-to-date clinical measurements, which are more likely to be available if there is already a clinical suspicion of sepsis. High-resolution data can potentially mitigate this problem and provide more timely prediction.

Although our algorithm was designed to predict new sepsis, those with positive risk assignments (score of 0.45 or higher) were associated with worse outcomes. Risk of death was over two-fold higher among those who had high-risk scores but did not develop sepsis (false positives) compared with those who had low risk scores but developed sepsis (false negatives). Many of the input features from the EMR (e.g., lactate) are not specific to sepsis and just indicate poor tissue perfusion. The same is true of high frequency variables like multiscale entropy; loss of organ-organ coupling is a sign of critical illness. It is possible that our algorithm can be extrapolated to all ICU patients to predict clinical decompensation agnostic of cause, but this would require further research.

Much of the contemporary focus in sepsis management is early intervention. AISE shifts the focus toward sepsis interdiction—identifying candidates for treatments before organ failure becomes established and before tissue sampling would be meaningful—thereby mitigating the cost, morbidity, and mortality burden of sepsis care. This interdiction system will allow caregivers to identify and treat patients with IV antibiotics, fluids, and other adjunct therapies based on a reliable estimate of their likelihood of developing sepsis in the near future.

AISE approaches have the potential to predict (and interdict) other forms of physiologic decompensation. Shared general experience around alerts and alarms makes it unlikely that simple notification of a bedside staff member will maximize the usefulness of this decision support approach. More likely, notification of a clinician that there is a prediction and the basis for that prediction will prompt an immediate focused review of a patient's physiology. There is no requirement that the clinician be at the bedside; indeed, our initial implementations will leverage a remote monitoring team precisely to avoid further burdens to the bedside staff. There are no restrictions on how—and to whom—the alerts can be transmitted: facilities can choose whom will be alerted based on local factors depending on their available resources and alert volume. We expect that healthcare systems with high numbers of alerts may use a tele-ICU system as an added monitoring “layer,” allowing bedside staff more time to provide quality care and decrease alarm fatigue.

This study comes with some limitations. The data were analyzed retrospectively using EMR data not originally designed for the analyses performed. However, this authenticates our analysis; it confirms its utility in a real-world clinical setting, showing good performance even in the presence of missing data. The retrospective design also means that suspicion of infection had to be inferred from systematic criteria, which may not reflect the true rationale of care in all patients. However, chart review was conducted on a select group of 100 patients with sepsis to validate our results, and our method was accurate in that sub-cohort (over 99% accuracy). The model used was trained on EMR data entered by bedside nurses, which may confer some recall and information bias. For instance, BP documentation by humans can be biased toward normal when compared with corresponding BP waveforms (21), in part due to back documentation of past data. However, these flawed data points are appropriate to use in our model since they contain predictive information when combined with other measurements.

Prediction is clearly less important than interdiction: it is not enough to know, we have to take actions that enhance patient-centered outcomes. Accordingly, we will first explore our algorithm's ability to identify the source of sepsis in those with risk scores above 0.45. This iteration of AISE will also be trained and validated on datasets accumulated in other hospitals. Second, AISE accuracy will be prospectively validated for real-time prediction in the clinical setting. We intend to let usual care proceed ignorant of the sepsis score while independent and isolated adjudicators knowing the sepsis score (experienced clinicians), but blinded to the decisions of the bedside team will be asked if and when the patient is sufficiently ill to interdict. Finally, a clinical intervention trial would assign patients to AISE (vs best care lacking AISE monitoring), followed by antibiotic and fluid administration depending on the risk score and the predicted infectious source. Such a trial could follow a stepped wedge design, under which the AISE algorithm is sequentially but randomly introduced to multiple units within one or more hospitals over a period of time. Primary outcomes of interest may include the number of vasopressor and ventilator-free days, with mortality and length of hospital stay as secondary outcomes of interest.”

CONCLUSIONS

In this two-center retrospective study, we demonstrate that high-performance models can be constructed to predict the onset of sepsis by combining data available from the EMR and high-resolution time series dynamics of BP and HR. Predictive performances of these models are inversely proportional to the lead time of prediction. Patients who are incorrectly labeled as those who will develop sepsis confer significant mortality, making this tool potentially useful in other clinical syndromes and disease processes.

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