Predictive Models for Severe Sepsis in Adult ICU Patients

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***Abstract* – Intensive Care Unit (ICU) patients have significant morbidity and mortality, often from complications that arise during the hospital stay. Severe sepsis is one of the leading causes of death among these patients. Predictive models have the potential to allow for earlier detection of severe sepsis and ultimately earlier intervention. However, current methods for identifying and predicting severe sepsis are biased and inadequate. The goal of this work is to identify a new framework for the prediction of severe sepsis and identify early predictors utilizing clinical laboratory values and vital signs collected in adult ICU patients. We explore models with logistic regression (LR), support vector machines (SVM), and logistic model trees (LMT) utilizing vital signs, laboratory values, or a combination of vital and laboratory values. When applied to a retrospective cohort of ICU patients, the SVM model using laboratory and vital signs as predictors identified 339 (65%) of the 3,446 patients as developing severe sepsis correctly. Based on this new framework and developed models, we provide a recommendation for the use in clinical decision support in ICU and non-ICU environments.**

Index Terms – ICU, Machine Learning, Predictive Monitoring, Prediction, Risk, Severe Sepsis.

INTRODUCTION

Severe sepsis, a systemic response to infection complicated by organ dysfunction, is a common cause of hospital morbidity and mortality [1]. Much work is being done to further model and predict the outcomes for patients with signs of infection or those who may be vulnerable to such events. Unfortunately, the systemic inflammatory response syndrome (SIRS) criteria which are used to diagnose severe sepsis may miss as many as 1 in 8 cases and predict outcomes poorly [1, 2]. Therefore, improved characterization of the systemic inflammatory response and factors that identify and risk-stratify patients with severe sepsis while they are in the hospital are needed.

Lactate is the end product of cytosolic glucose metabolism without the use of the mitochondria, a largely inefficient process. While some tissues function using anaerobic metabolism (such as skeletal muscle), most clinical scenarios in which lactate is overproduced signifies cellular disarray. Typically this is due to global or regional hypoxia, or deficits in lactate clearance. Septic shock may occur when oxygen utilization is compromised for a variety of reasons and lead to hyperlactatemia [3]. Regardless of the physiology, the data are clear that admission lactate concentrations, maximum lactate concentrations, and time to normalization of lactate concentrations correspond with hospital mortality from severe sepsis [4].

In this work, we define severe sepsis as the presence of 1) suspected infection and 2) hyperlactatemia as evidenced by blood culture acquisition and a concurrent lactate concentration of at least 4 mmol/L. Using ICU admitted patients with such criteria, we seek to investigate which physiological patterns or clinical events precede severe sepsis and better risk-stratify patients potentially vulnerable to severe sepsis.

LITERATURE REVIEW

The task of prognosis is a crucial component in critical care to predict the future health status of a patient. Prognostic models improve the accuracy of life expectancy estimation in critical clinical decisions and are shown to be superior to physicians' prognostication alone [5]. In critical care settings such as the ICU, these models are usually concerned with identifying important outcomes such as complications, death, or other long-term sequelae [6, 7]. Prognostic risk models have been employed in critical care settings since the 1980s to aid in informed treatment decisions [8], improve the quality of care [9, 10], and make end-of-life care decisions [11, 12].

Different techniques have been utilized to construct models that classify patients into prognostic categories. Multiple logistic regression models dominate clinical prognostic models for the ICU [8, 13-15], largely as a result of the simplicity of its application, the widely available software packages, the history of usage with successful results in the field, and the ability to statistically interpret model parameters [16]. However, logistic regression is not able to identify non-linear structures in the dataset, and its results may be invalidated when its assumptions are not met in practice. Other methods stem from artificial intelligence techniques such as support vector machines [7]. Most of these techniques produce black-box models, generally with improved accuracy but at the cost of interpretability of the parameters and the traceability of the model process. These

drawbacks have limited the popularity of black-box models in domains such as medicine where interpretability is crucial.

In this work, we propose to develop predictive models for severe sepsis, a significant cause of morbidity and mortality in ICU patients. Prior studies have investigated models to predict both the mortality of patients with sepsis and the incidence of severe sepsis in patients [6, 7]. A 2012 study of severe sepsis and mortality used logistic regression and factor analysis to develop a predictive model of mortality with multiple lab values and several Sequential Organ Failure Assessment (SOFA) scores as variables [6]. This study achieved a higher sensitivity than that obtained by applying the APACHE II score's risk-of-death (ROD) formula [17], a metric more commonly used to indicate the severity of a patient's condition. In [7], a classification method with support vector machines (SVM) to predict mortality in sepsis patients using only median lactate level, mean arterial pressure, and median absolute deviation of respiratory rate.

Several previous efforts have attempted early recognition of sepsis [18-22]. One such study predicted severe sepsis in neonatal patients using models such as average one dependence estimator (AODE), naïve Bayes (NB), and random forest (RF) [19]. The models with the best performance outperformed the actual decisions made by physicians for the patient cohort. A drawback to this study, however, is the low number of patients included (n=299). Another study used only heart rate characteristics to predict severe sepsis in neonatal infants, developing a monitoring score that corresponded with a relative mortality reduction of 20% [18]. In [20], an Infection Probability Score (IPS) for adult patients is devised based on temperature, heart rate, respiratory rate, white blood cell count, C-reactive protein, and (SOFA) scores. Models incorporating principal component analysis (PCA) and SVM using data for RR intervals and PPG waveforms performed well, but the authors of the study noted limitations due to a small sample of patients (n=27) [21]. Another study that applied SVM on a larger sample of patients (n=1000) also performed well in predicting severe sepsis, but the selected patients all had sepsis [22]. Another drawback to SVM models is lack of interpretability of individual features. Models based on regression trees have much lower performance scores than SVM models but can be easily understood and applied in practice by clinicians [23].

METHODS

I. Data Description

Retrospective data from the MIMIC-II research database [24] is used for our analysis. The MIMIC-II database encompasses a diverse and very large population of ICU patients. It also contains high temporal resolution data including lab results, electronic documentation, and bedside monitor trends and waveforms. From this database we extracted data for laboratory values, vital signs, blood cultures, age and length of stay [25].

The features include 12 laboratory values and four vital signs. From those features we calculated their median values and interquartile ranges (IQR) for the target and control groups. These features, along with their median values and IQR, separated by target and control groups, are listed in Table I. The laboratory values are taken as part of routine chemistry and hematology blood tests. We originally considered 13 additional laboratory values and one additional vital sign, but after initial analysis of the features, we selected only those that were recorded for at least half of the patients during the specified time period of 24 to two hours prior to time of event.

II. Patient Selection Criteria

Patients considered in this paper were at least 18 years old and were in the ICU for at least 48 hours. From this subset, we selected a target group to include patients who met our definition of severe sepsis (lactate concentration of at least 4 mmol/L within 24 hours of blood culture acquisition). Patients were excluded if they had a high lactate and blood culture taken more than 24 hours apart or if the blood culture did not have a time stamp. The control group was selected from a portion of the remaining patients. Both the target and control group were further reduced if patients did not have measurements for at least 50% of the selected features during the specified period of 24 to two hours prior to time of event. After reduction, the analysis included 521 patients in the target group and 2,925 patients in the control group.

TABLE I
LIST OF FEATURES

FEATURES	CONTROL, N=2,925	TARGET, N=521
Laboratory Values – Median (IQR)		
Anion Gap	13.0 (11.0, 15.0)	16.0 (14.0, 20.0)
Bicarbonate	25.0 (23.0, 28.0)	21.0 (18.0, 25.0)
BUN	20.0 (12.3, 33.0)	32.0 (19.0, 52.0)
Calcium	8.3 (7.9, 8.8)	8.15 (7.6, 8.8)
Creatinine	0.9 (0.7, 1.3)	1.5 (1.0, 2.5)
Glucose	121.0 (103.0, 145.0)	132.0 (104.0, 173.0)
Hematocrit	30.0 (27.3, 33.2)	30.7 (27.4, 34.4)
Hemoglobin	10.3 (9.3, 11.5)	10.4 (9.4, 11.7)
Magnesium	2.0 (1.9, 2.2)	2.0 (1.8, 2.3)
Phosphate	3.2 (2.5, 3.9)	3.9 (3.0, 5.2)
Platelet Count	189.0 (133.0, 259.0)	156.0 (92.0, 252.5)
WBC	10.8 (8.4, 14.2)	13.1 (8.1, 20.3)
Vital Signs – Median (IQR)		
Blood Pressure	120.0 (106.0, 136.0)	104.0 (92.8, 120.0)
Heart Rate	84.0 (73.0, 96.0)	97.0 (82.0, 113.0)
Respiratory Rate	20.0 (16.0, 24.0)	22.0 (18.0, 27.0)
Temperature	98.6 (97.7, 99.5)	98.8 (97.2, 100.3)

Abbreviations: BUN- blood urea nitrogen; WBC- white blood cell count

III. Data Preprocessing

The data values for each patient were binned into half-hour intervals. If a patient had multiple measurements for a particular feature during a half-hour period, the mean of the measurements was recorded. The time of event, t(0), was determined for patients in both the target and the control group. For the target group, t(0) was defined as the first instance of high lactate that occurred within 24 hours of a blood culture. For the control group, t(0) was a randomly selected time at least 48 hours after the patient was admitted to the ICU. Measurements taken between 24 and two hours before t(0) were included in the analysis. Measurements recorded within two hours of t(0) were excluded. These measurements are likely to skew the other data for patients with severe sepsis, as discussed in [23]. Additionally, the objective of this paper is to predict severe sepsis in advance of an episode, so considering measurements within two hours would limit the predictive capability of the models.

All features were capped at the 1st and 99th percentiles to control for extreme outliers. Missing values were imputed using k-nearest neighbors. For each laboratory value, we calculated the median, minimum, and maximum measurement for each patient from the 24-to-2 hour period for a total of 36 derived laboratory features. For each vital sign, we calculated the median, minimum, maximum, and standard deviation for each patient from the 24-to-2 hour period for a total of 16 derived vital sign features.

RESULTS

We built three models on each of the datasets described above: logistic regression, support vector machines, and logistic model trees. For each method, we deliberately set the output of those models to be probabilities instead of classes. This approach allows us to derive metrics for both regression and classification problems. The metrics are sensitivity, specificity, positive predictive value (PPV), negative predicted value (NPV), and area under curve (AUC).

The metrics were derived using a 10-fold cross validation strategy with stratified sampling to maintain a proportion of target group in the training and test sets consistent with that in the entire dataset.

As an additional metric for evaluating the model, we developed a quantile evaluation method. Predictions were split into 10 quantiles, and for each quantile we calculate the percent of severe sepsis patients in that particular quantile. We are most interested in the precision in the last two quantiles, i.e., the precision of classification for patients assigned a high-risk score.

I. Logistic Regression

Logistic regression is a widely used method for analyzing clinical data and is suitable as a baseline model for comparison with other machine learning techniques. The initial laboratory values, vital signs, and combined datasets contain 36, 18, and 52 derived features, respectively. To reduce features, we first applied the *best-first search* method which performs a greedy search algorithm over the features using forward selection. We also examined the variance inflation factor (VIF) of each feature to remove potential multicollinearity. Features with VIF higher than five were taken out. Finally, we utilized Bayesian Information Criterion (BIC) using the backward elimination for model selection.

II. Support Vector Machines

Support vector machines (SVM) are another common machine learning method for classifying categorical data [26]. SVM has an advantage over logistic regression in that it can account for non-linear relationships between explanatory and response variables. However, SVMs lack the transparency and clinical interpretability of logistic regression and tree-based models.

To reduce the feature space, we applied a selection algorithm that ranks attributes by the squared weight assigned by an SVM classifier. We selected features and kept the same number of variables in each data set as in logistic regression model (12 for combined data, nine for laboratory data, and four for vital signs data). We used the radial basis kernel function with cost equal to 10. Ten-fold cross validation was applied to calculate the average metric scores. Similarly to the logistic regression models, we used quantile method as an additional evaluation technique.

III. Logistic Model Trees

Logistic Model Trees, a modeling technique designed to combine the predictive accuracy of logistic regression model and simple interpretation of classification trees, is also explored for prediction of severe sepsis. LMT grows a standard classification tree while building a logistic regression model at each node. As a result, the output is a score between zero and one instead of a class. Because the model outputs scores instead of classes, we could apply the metrics for regression problem as mentioned above to the model. We used Akaike Information Criterion (AIC) with backward elimination to reduce features in the logistic regression model.

IV. Model Performance

The metrics shown in Table II are used to evaluate the performance of each model. All methods performed best with the combined laboratory and vital sign data. SVM performed better than LR and LMT for vital sign only and combined data models. However, it performed comparably with the LMT model for clinical laboratory values.

Table III contains the list of features and their coefficients for the three logistic regression models. All the features in the laboratory only model were preserved in the combined model. For vital signs, temperature dropped out of the combined model after the feature selection was applied.

TABLE II
DERIVED MODEL RESULTS

Laboratory Values Only			
	LR	SVM	LMT
Sensitivity	0.546	0.605	0.588
Specificity	0.920	0.927	0.929
PPV	0.563	0.609	0.610
NPV	0.915	0.926	0.923
AUC	0.827	0.840	0.862
Vital Signs Only			
	LR	SVM	LMT
Sensitivity	0.436	0.585	0.442
Specificity	0.899	0.935	0.906
PPV	0.447	0.629	0.467
NPV	0.894	0.923	0.896
AUC	0.759	0.840	0.759
Combined Laboratory and Vital Sign Data			
	LR	SVM	LMT
Sensitivity	0.603	0.642	0.609
Specificity	0.932	0.936	0.933
PPV	0.624	0.651	0.631
NPV	0.926	0.933	0.927
AUC	0.877	0.871	0.882

Abbreviations: LR- logistic regression; SVM- support vector machine; LMT- logistic model tree; PPV- positive predictive value, NPV- negative, predictive value; AUC- area under the curve

The positive coefficients for glucose, white blood cell count, and respiratory rate correspond with physiological increases that frequently occur during inflammatory states such as severe sepsis. Similarly, the standard deviation of temperature is likely significant due to temperature fluctuations that occur as a physiological response to infection.

The negative hemoglobin coefficient may reflect decreased oxygen carrying capacity that occurs during severe sepsis as a result of complications such as disseminated intravascular coagulation and which often requires blood transfusion [27]. Conversely, a higher concentration of hematocrit may be linked to extravascular fluid losses that occur in severe sepsis and subsequent hemoconcentration. The models also include both the minimum and maximum for magnesium with opposite coefficients, indicating that a significant change in magnesium in either direction corresponds to a higher likelihood of severe sepsis [28].

The positive coefficient of anion gap, which increases in the setting of increased unmeasured anions including lactate, and the negative coefficient of bicarbonate, which decreases in the setting of acidosis, both correspond to physiological changes associated with lactic acidosis. Low blood pressure may lead to hypoperfusion and decreased end-organ oxygen delivery as occurs during severe sepsis and is manifested as hyperlactatemia. Hypoperfusion during severe sepsis may also lead to low flow pre-renal states that lead to renal insufficiency and associated elevated creatinine concentrations and heart rate may increase in order to maintain adequate cardiac output.

TABLE III
FEATURES AND COEFFICIENTS FOR LOGISTIC REGRESSION MODELS

Laboratory Values Only	
Features	Coefficients
Intercept	-4.439
Glucose (med)	0.005
Bicarbonate (med)	-0.062
Anion gap (min)	0.165
Magnesium (min)	-1.550
Hemoglobin (min)	-0.551
WBC (min)	0.036
Creatinine (max)	0.226
Magnesium (max)	0.911
Hematocrit (max)	0.228
Vital Signs Only	
Features	Coefficients
Intercept	-2.355
Temp. (sd)	0.336
Heart rate (min)	0.045
Blood pressure (min)	-0.042
Respiratory rate (min)	0.070
Combined Data	
Features	Coefficients
Intercept	-6.300
Glucose (med)	0.006
Bicarbonate (med)	-0.051
Anion gap (min)	0.140
Magnesium (min)	-1.235
Hemoglobin (min)	-0.470
WBC (min)	0.024
Creatinine (max)	0.269
Magnesium (max)	0.924
Hematocrit (max)	0.215
Heart rate (min)	0.041
Blood pressure (min)	-0.035
Respiratory rate (min)	0.067

Abbreviations: med, median; min, minimum; max, maximum; sd, standard deviation; WBC, white blood cell count

Further analysis of the data was performed by dividing patients into ten quantiles according to their predicted risk score for severe sepsis. The mean risk score of each quantile was then compared to the actual percentage of patients in that quantile who had severe sepsis. The quantile plots are shown in Figures 1-3. The x-axis refers to the mean value of each quantile interval while the y-axis refers to the percentage of patients within a given quantile interval who have severe sepsis. Points closer to the 45-degree dashed line indicate a more accurate predictive model. Points are below the dashed line if the model overestimates the risk score. The models built with vital signs and laboratory datasets have greater variation than the combined model. The three models perform similarly for the combined model, though SVM performs better than the other two. Logistic regression and LMT tend to overestimate the risk score for higher quantiles. In the laboratory model, logistic regression has less variation than the other two, and LMT tends to overestimate the risk score when the risk quantile is high.

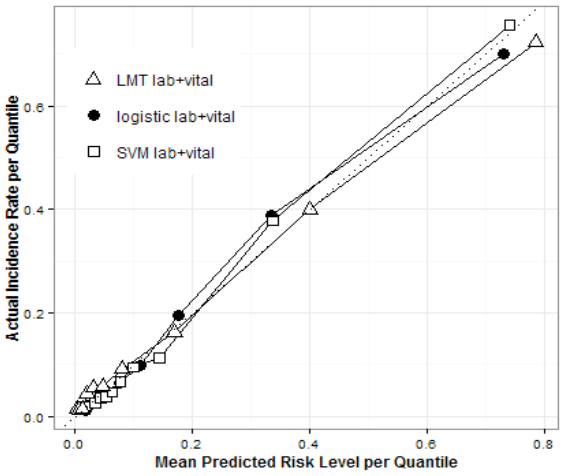

FIGURE 1
QUANTILE PLOT FOR LAB + VITAL MODELS

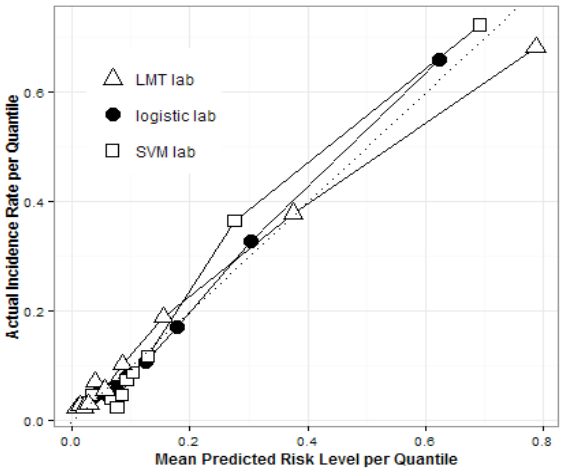

FIGURE 2
QUANTILE PLOT FOR LAB ONLY MODELS

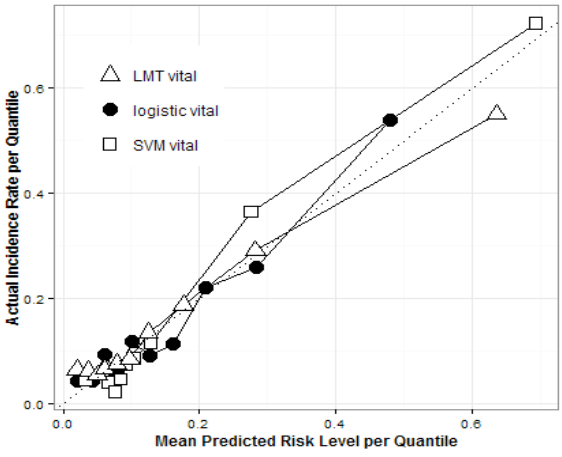

FIGURE 3
QUANTILE PLOT FOR VITAL SIGN ONLY MODELS

To further evaluate the accuracy of the risk scores, we compared percent of severe sepsis patients in each quantile with the mean predicted risk score for each quantile. The results suggest our risk scores represent actual risk of getting severe sepsis well with the last quantile capturing a high proportion of severe sepsis patients.

DISCUSSION

The work shows significant promise for the development of a new framework for the detection of severe sepsis. SVM outperforms LR and LTM in terms of predictive power. However, SVM lacks the clinical transparency and interpretability of regression and tree based methods. Future work will evaluate the clinical utility of the developed models and predictors.

Another limitation of this work is that we only consider models using 24 hours of data before the severe sepsis event. We removed two hours of data before the event to prevent bias caused by data too close to the time of event. In future work, we will build models that look from 48 to 24 hours before the event to see if less recent data could be utilized in predicting severe sepsis. Furthermore, we would like to derive separate models for shorter intervals during 48 hours. We hypothesize that different features may appear predictive in different time to event intervals.

Meanwhile, we will also explore more robust feature selection methods combined with clinical expertise to improve our model. We also hypothesize that comorbidities could be an important factor to consider when predicting severe sepsis. Also, considering the fact that only seriously ill patients have invasive measurements taken, binary indicators for missing values could be developed for those features to better present the condition of those patients.

The appropriate predictive model is also highly dependent on the clinical environment and workflow. In ICUs, patients are continually monitored and can have real-time risk computation based on bedside physiological monitoring. However, patients on the floor also experience significant morbidity and mortality from sepsis, which could benefit from models that can be applied within the context of an Electronic Health Record System.

CONCLUSION

Prediction of severe sepsis is a challenging domain. In this paper, we propose an alternative framework for earlier identification of severe sepsis using suspected infection and hyperlactatemia. Our models choose several practical factors to monitor and predict those patients at high risk of developing severe sepsis. One limitation of this work is that we do not look at patient outcomes such as lactate clearance or mortality. In future work, we will adapt our framework and build models to identify patients at higher risk of mortality within the severe sepsis population. The proposed framework and predictive models have the potential to aid in clinical decision making in ICU and non-ICU environments

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