Using machine learning to diagnose bacterial sepsis in the critically ill patients

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Abstract. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Early antibiotic therapy to patients with sepsis is necessary. Every hour of therapy delay could reduce the survival chance of patients with severe sepsis by 7.6%. Certain biomarkers like blood routine and C-reactive protein (CRP) are not sufficient to diagnose bacterial sepsis, and their sensitivity and specificity are relatively low. Procalcitonin (PCT) is the best diagnostic biomarker for sepsis so far, but is still not effective when sepsis occurs with some complications. Machine learning techniques were thus proposed to support diagnosis in this paper. A backpropagation artificial neural network (ANN) classifier, a support vector machine (SVM) classifier and a random forest (RF) classifier were trained and tested using the electronic health record (EHR) data of 185 critically ill patients. The area under curve (AUC), accuracy, sensitivity, and specificity of the ANN, SVM, and RF classifiers were (0.931, 90.8%, 90.2%, 91.6%), (0.940, 88.6%, 92.2%, 84.3%) and (0.953, 89.2%, 88.2%, 90.4%) respectively, which outperformed PCT where the corresponding values were (0.896, 0.716, 0.952, 0.822). In conclusion, the ANN and SVM classifiers explored have better diagnostic value on bacterial sepsis than any single biomarkers involve in this study.

Keywords: Sepsis, Bacterial Sepsis, Machine Learning, Artificial Neural Network, Support Vector Machine, Diagnostic Value

1 Introduction

Sepsis is a complex, fatal disease and mainly occurs after serious infections. The latest International Consensus defined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It is one of the most common reasons for intensive care unit (ICU) attendance, and can be easily found in non-ICU departments as well (10.9% of hospitalizations in U.S.; 95% CI) [2, 3]. Meanwhile, it is associated with high mortality, 34.7% to 52.0% of inpatient deaths in U.S. (95% CI) occurred among patients with sepsis [3].

In clinical practice, it is difficult to diagnose sepsis accurately. In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine defined

sepsis as infection, or suspected infection, meeting two or more systemic inflammatory response syndrome (SIRS) criteria (Sepsis 1.0) [4]. However, latter studies criticized that the Sepsis 1.0 criteria lacked both sensitivity and specificity [5, 6]. After the release of the Sepsis 2.0 criteria, which was too complicated and impractical for clinic usage, the new Sepsis 3.0 criteria was released in February 2016. The Sequential Organ Failure Assessment (SOFA) score in ICU or the qSOFA score outside ICU were recommended to replace SIRS criteria. Although Seymour's research showed that SOFA and qSOFA score has a higher predictive validity for in-hospital mortality [7], the reliability is uncertain and should be tested and verified by future research. Therefore, patients meeting any of those criteria could be considered as suspected sepsis.

Guidelines recommend that the early antibiotic therapy should be administered to patients with suspected sepsis [8]. Every hour of antibiotic usage delay would decrease the survival chance of patients with severe sepsis by 7.6% [9]. However, since it takes at least 48 hours to obtain the results of a blood culture test, which is the gold standard of bacteria detection, even for an experienced physician, it is difficult to choose the effective antibiotics in early treatment. Usually, physicians have to speculate the possible source of infection under limited resources, and then be forced to use several types of empiric, broad-spectrum antibacterial agents in order to cover all the possible bacteria. Yet, the excessive usage of antibiotics may lead to unwanted liver and kidney damage, and extra medical spending as well [10].

There are certain biomarkers that can be referenced in the early hours of sepsis infection, such as blood routine (include total and differential white blood cell (WBC) count, platelet count, erythrocyte & reticulocyte count, and hemoglobin), and C-reactive protein (CRP), but their sensitivity and specificity are not sufficient for physicians to distinguish bacterial infection. Specifically, the sensitivity and specificity of CRP and WBC are (75%, 67%) and (46.4%, 46.7%) respectively [11]. Platelet Count (PLT) and Hemoglobin (Hgb) were also proven to be associated with the occurrence and development of disease [12, 13] but cannot diagnose bacterial infection alone [14].

On the other hand, procalcitonin (PCT) showed the best diagnostic value so far, with a sensitivity of 88% and a specificity of 81% [15] and had the ability to identify Gram-positive and Gram-negative bacterial infection [16]. Therefore, the newest guideline recommends using PCT level to diagnose sepsis. However, some studies also pointed out that PCT level may increase after surgery [17], trauma [18], heatstroke [19], burn [20], severe pancreatitis [21], anaphylactic shock [22] or cardiogenic shock [23] without obvious infection, which would affect its diagnostic value on sepsis.

Artificial neural networks (ANN), as one of the machine learning technologies, can be used for classification in this context. The structure of ANN is similar to the human brain, with nodes and links that simulate the functions of neuron bodies, axons, and dendrites. Some research showed that ANN exhibit better performance than other

statistical classifier methods [24, 25]. Lammers et al. [26] showed that ANN was capable of discriminating wound infection with sensitivity of 70% and a specificity of 76% (as compared to 54% and 78% of physicians), and Heckerling et al. [27] developed an ANN model with sensitivity of 82.1% and specificity 74.4% for identifying urinary tract infection. Thus, ANN classifier may have the capacity to indicate bacterial infection with the various infection-related biomarkers as input. Similar to ANN, support vector machine (SVM) is a supervised machine learning method where the training a SVM model is a process trying to identify the widest gap that can separate the data mapped in a high-dimensional coordinate system by different categories [28]. Previous researches showed the SVM classification models had powerful performances on tasks related to biomarker data [29–31]. Besides, random forest (RF), developed by Breiman [32], is an ensemble learning method that using bagging algorithm to build multiple decision trees ensemble with random subsets and variables. Studies showed that RF method could predict diseases with good accuracy [33–36]. In the paper, these three machine learning methods are exploited to diagnose bacterial sepsis in the critically ill patients.

2 Methods

2.1 Subjects

EHR data of 185 inpatients in the ICU and Medical ICU (MICU) departments with suspected sepsis in the General Hospital of Guangzhou, China, were collected through the convenience sampling method in this study. 13 patients among were diagnosed with heatstroke; 27 with trauma; 9 with severe pancreatitis and 15 with postoperation. Meanwhile, 102 cases of them were diagnosed with bacterial sepsis by a physician through the medical records.

The inclusion criteria are as follows: 16–80 years of age with a suspected diagnosis of infection (admitting or discharge diagnoses for infection or taking antibiotic treatment during hospitalization), or fulfilling SIRS criteria or the SOFA score >2; with the results of blood routine, PCT, CRP, and blood culture tests. Subjects will be excluded if they are pregnant; have any diseases that affect their immune system seriously (e.g., autoimmune disease, AIDS, cachexia); taking immunosuppressive therapy; with a discharge diagnosis of virus or fungal infection.

2.2 Data collection

General information (gender, age), medical history, progress note (temperature, heart rate, respiratory rate, blood pressure, Glasgow coma scale, SOFA score), prescription, and admitting and discharge diagnoses of subjects were recorded through a de-identified processing following the HIPAA Privacy Rule's De-Identification Standard [37]. The following biomarker measurements will be obtained from the clinical laboratory: Blood Routine Examination (Total leukocyte count, Neutrophils Count, Eosinophils Count, Lymphocytes Count, Monocytes Count, Basophils Count,

Erythrocyte Count, Hemoglobin, Hematocrit Value, Platelet Count), PCT, CRP, PaO2, FIO2, Bilirubin, and Creatinine.

3 Dataset

Generally, values of blood routine, PCT and CRP will be applied as the input; attributes that can be calculated from other test results in the blood routine test have been ignored by the study, such as Neutrophils percent (NE/WBC), Eosinophils percent (EOS/WBC), Basophils percent (BAS/WBC), Lymphocytes percent (LYM/WBC), Monocytes percent (MON/WBC), Mean Corpuscular Volume (Hct/RBC), Mean Corpuscular Hemoglobin (Hgb/RBC), and Mean Corpuscular Hemoglobin Concentration (Hgb/Hct). Since gender or age could affect the normal range of some biomarkers, they were considered as inputs as well. Thus, there were fourteen inputs and two outputs contained in the final dataset (Table 1). Also, a normalization method was applied to scale the numerical values into the range [0,1].

Table 1. Dataset

Input	Attributes	Input values of the algorithms
1	Gender	1 (Male), 0 (Female)
2	Age	Normalized to [0,1]
3	Total Leukocyte Count (WBC)	
4	Neutrophils Count (NE)	
5	Eosinophils Count (EOS)	
6	Basophils Count (BAS)	
7	Lymphocytes Count (LYM)	
8	Monocytes Count (MON)	
9	Erythrocyte Count (RBC)	
10	Hemoglobin (Hgb)	
11	Hematocrit Value (Hct)	
12	Platelet Count (PLT)	
13	Procalcitonin (PCT)	
14	C-reactive protein (CRP)	
Output	Attributes	Output values of the algorithms
1	Bacterial sepsis	1 (Yes), 0 (No)

3.1 Machine learning models

A backpropagation neural network model of fourteen neurons in the input layer, seventeen in the first hidden layer, two in the second hidden layer and one in the output layer was trained through the Fast Artificial Neural Network Library (FANN) [38] using linear activation function at the output and sigmoid activitaiton functrion at the hidden layer (Fig.1).

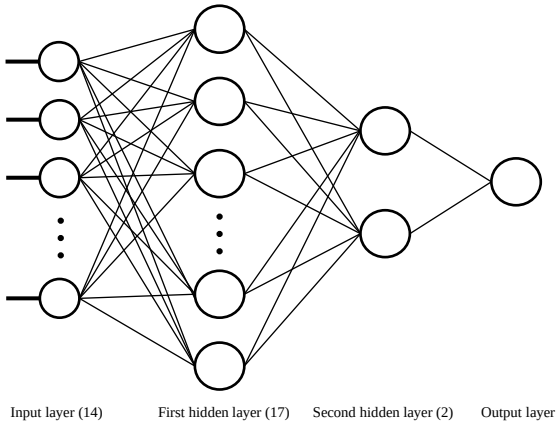

Fig. 1. The neural network structure.

The SVM classifier model was trained using the Matlab LIBSVM toolbox [39]. The parameters c=1.414 and g=4 were optimized by a grid search under a 10-fold cross-validation process. The RF model was built using the Matlab RF tool [40, 41], the tree number was set to 800 after a parameter performance evaluation under a 10-fold cross-validation process.

3.2 Evaluation

The performance of the classifications was tested using leave-one-out cross-validation (LOOCV), where the classifier used single observation to test the performance of model trained by the remaining observations. The process was then repeated to ensure that all observation was tested. Then, sensitivity, specificity, precision, and accuracy were calculated from the results. In addition, receiver operating characteristic (ROC) curves were plotted, and AUC was calculated to determine the overall performance of the machine learning models. Meanwhile, in order to compare the diagnostic values of the machine learning methods and the biomarkers, the ROC curve was studied for each biomarker, and the sensitivity, specificity, precision, and accuracy of the three machine learning methods with the largest AUC were determined based on the best cutoff point that maximizes the Youden's index (i.e. sensitivity + specificity - 1) [42].

4 Result

The ROC curves of the selected biomarkers have been plotted as Fig. 2. PCT got the highest diagnostic value, with an AUC of 0.896 (95% confidence interval [CI], 0.81 to 0.942) via biomarkers, followed by CRP (AUC, 0.832; 95% CI, 0.7743 to 0.890) and N (AUC, 0.681; 95% CI, 0.603 to 0.759). At a cutoff value at 8.56 ng/ml of PCT, 87.5 mg/l of CRP, and 14.34 of Neutrophil count, they yielded sensitivity,

specificity, and accuracy of (71.6%, 95.2%, 82.0%); (75.5%, 78.3%, 76.8%); and (56.9%, 75.0%, 64.9%), respectively. PCT was the most powerful biomarker for diagnosing sepsis syndrome in this analysis.

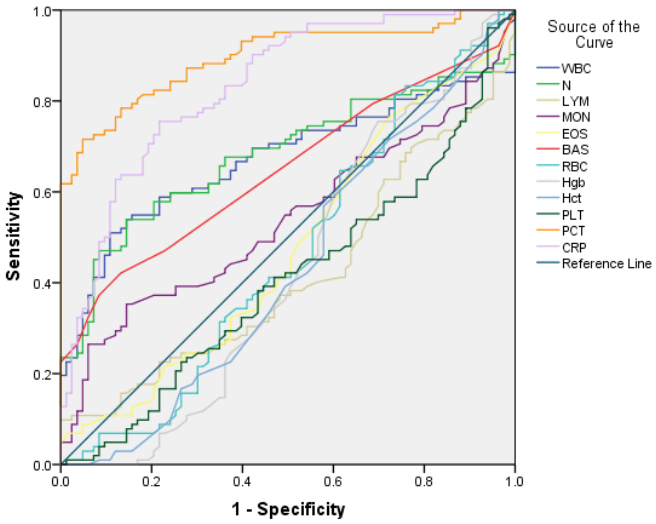

Fig. 2. ROC Curves of biomarkers

Table 2. AUC and CI of biomarkers

Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
WBC	0.672	0.593	0.751
NE	0.681	0.603	0.759
LYM	0.418	0.336	0.500
MON	0.540	0.457	0.623
EOS	0.476	0.392	0.561
BAS	0.648	0.570	0.727
RBC	0.462	0.376	0.547
Hgb	0.429	0.343	0.515
Hct	0.431	0.346	0.516
PLT	0.408	0.326	0.490
PCT	0.896	0.851	0.942
CRP	0.832	0.774	0.890

To explore the diagnostic performance between single biomarker and machine learning models, ROC curves of PCT, ANN, SVM, and RF were plotted (Fig. 3). As shown in Table 3, all three machine learning models yielded a higher AUC value (ANN: 0.931, 95% CI 0.889–0.973; SVM: 0.940, 95% CI 0.903–0.977; RF: 0.953, 95% CI 0.924-0.981) than the most valuable biomarker, PCT (0.896, 95% CI 0.851–0.942).

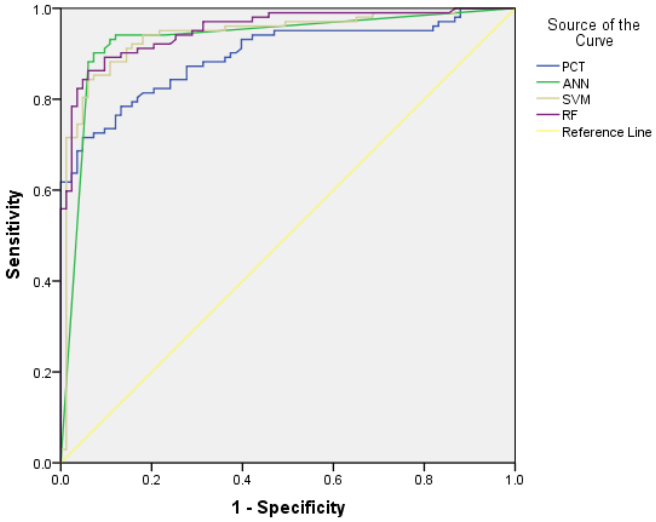

Fig. 3. Fig. 4. ROC Curves of PCT, ANN, and SVM

Table 3. AUC and CI of ANN, SVM, PCT and CRP

Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
PCT	0.896	0.851	0.942
ANN	0.931	0.889	0.973
SVM	0.940	0.903	0.977
RF	0.953	0.924	0.981

Table 4. Performance of ANN, SVM, RF, and PCT

	ANN	SVM	RF	PCT (Cutoff = 8.56)	PCT (Cutoff = 3.40)
True positive	92	94	90	73	90
False positive	7	13	8	4	28
True negative	76	70	75	79	55
False negative	10	8	12	29	12
Accuracy	90.8%	88.6%	89.2%	82.2%	78.4%
Sensitivity	90.2%	92.2%	88.2%	71.6%	88.2%
Specificity	91.6%	84.3%	90.4%	95.2%	66.2%

Both the accuracy and sensitivity of ANN (90.8%, 90.2%), SVM (88.6%, 92.2%), and RF(89.2%, 88.2%) were better than those of PCT (82.2%, 71.6%) at a cutoff value of 8.56 ng/ml determined by Youden's index (see Table 4), where the specificity

of ANN (91.6%), SVM (84.3%), RF (90.4%) were lower than that of PCT (95.2%). However, when we set the cutoff PCT concentration with identical 88.2% sensitivity at 3.40 ng/mL, both its accuracy (78.4%) and specificity (66.3%) were clearly lower than those of ANN, SVM, and RF models (see Table 4).

5 Discussion

The results of this study show that machine learning methods, ANN, SVM, and RF can be used to diagnose bacterial sepsis in the critically ill patients. The machine learning models classified ICU patients of sepsis and non-sepsis with AUC that ranged at 0.931 (ANN), 0.940 (SVM), and 0.953 (RF), indicating good diagnostic accuracy. These classification accuracies exceeded the most widely used biomarker, PCT, which had a ROC area of 0.896. It indicates that machine learning methods like ANN, SVM, and RF have the ability to identify certain characteristics from a variety of biomarkers and exhibit better performance than statistical classifier methods.

The current structure and variables settings of ANN and SVM model may not be the best combination that represents the full capacity. It is difficult to detect the best settings unless all possible structure and variables had been tested. Some tools have provided algorithms that can explore the best settings, but the effect still needs to be verified. For example, the FANN Toolbox [38] used in this study provide a topology training function (Cascade2) that can dynamically train the neural network. However, according to our work, the performance of Cascade structure was worse than the 14-17-2-1 structure we used, let alone lots of possible structures that are not explored in general. Another simple example is that many methods are available to determine the best c and g value when building a SVM classifier, such as Grid Search, Genetic Algorithm (GA) and Particle Swarm Optimization (PSO) method. However, out tests show that even though the overall performances of the SVM models built based on these methods were similar, the best c and g value generated by different methods could vary a lot. Meanwhile, when new data were added into models, the variables could be changed again. Therefore, it is a challenging task to find out or even evaluate the best structure and variables.

Moreover, the sample size of this study may still be not enough for the machine learning methods to identify sufficiently specific characteristics. Sepsis is always associated with other medical conditions, which in turn affects the biomarkers that diagnose sepsis [17–21]. In this study, the number of subjects with burn, anaphylactic shock or cardiogenic shock were lower than 10. Along with individual variations, the feature of these samples might not be learned by the algorithms completely. To solve this problem, it is necessary to enlarge the sample size in the future work. A sufficient sample size will not only resolve the current problem but also meet the requirements of applying more advanced methods in the fields of deep learning, e.g. stacked auto-encoder (SAE) [43] and multi-layer convolutional neural networks (CNNs) [44].

6 Conclusion

ANN, SVM, and RF methods were explored in this study for diagnosing bacterial sepsis in the critically ill patient. All the proposed classifiers, using 14 biomarkers as the input, evaluated by the leave-one-out cross-validation technique, showed better performance in AUC, accuracy, sensitivity and specificity, when compared to those obtained by using a single biomarker. This study has shown that ANN, SVM, and RF classifiers can improve the diagnostic quality of bacterial sepsis. However, studies with larger sample size are necessary in future study to improve the performance of classifiers. Further research on the structure and setting of the models in the machine learning methods concerned will also be conducted.

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