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Using Biochemical Indexes to Prognose Paraquat-Poisoned Patients: An Extreme Learning Machine-Based Approach

LUFENG HU[1], PANXIN YANG[2], XIANQIN WANG[3], FEIYAN LIN[4], HUILING CHEN[5], HONGCUI CAO[2], AND HAIYING LI[4]

[1]Department of Pharmacy, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China
[2]School of Laboratory Medicine and Life Sciences, Wenzhou Medical University, Wenzhou 325000, China
[3]Analytical and Testing Center, Wenzhou Medical University, Wenzhou 325035, China
[4]Laboratory of Internal Medicine, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou 325000, China
[5]Department of Computer Science, Wenzhou University, Wenzhou 325035, China

Corresponding authors: Huiling Chen (chenhuiling.jlu@gmail.com), Hongcui Cao (chc2016@sina.com), and Haiying Li (lihaiying123321@163.com)

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ABSTRACT The biochemical indexes are used to assess the hepatic and renal function of paraquat (PQ) poisoning patients. However, these indexes correlated with the prognosis of patients are unidentified. This paper aims to explore useful indexes from biochemical tests and to identify their predictive value. A total of 101 PQ poisoning patients including 51 dead patients and 50 survived patients is involved in this study. The biochemical indexes of PQ poisoning patients in different status are collected and analyzed by the independent-sample test. After that, Fisher scores feature selection is applied to screen prognostic factors from biochemical indexes. Based on the results of Fisher selection, an effective extreme learning machine (ELM) is applied to diagnose the prognosis status of PQ poisoning patients. The created ELM method is rigorously evaluated for accuracy, sensitivity, and specificity. The results show that there is statistical significance between dead and survived people in biochemical indexes ($P < 0.01$). Feature selection revealed that direct bilirubin, alanine aminotransferase (ALT), total bilirubin, aspartate aminotransferase (AST), the ratio of ALT/AST, and creatinine are the most crucial indexes, which correlated with the prognosis of PQ poisoning. The maximal classification accuracy is 79.6% when these six indexes are selected as the dataset. In conclusion, the biochemical test is related to the prognosis of PQ poisoning patients. It provides a new method for prognosis of PQ poisoning with feature selection and ELM model.

INDEX TERMS Extreme learning machine, biochemical index, paraquat, medical prognosis, patients.

I. INTRODUCTION

Paraquat (1,1′ -dimethyl-4,4′ -bipyridium dichloride, PQ) is a widely used herbicides with its safety in seedlings, and good affectivity in weeding. Meanwhile, it saves much time and money. However, it is an extremely toxic pesticide for human. The oral lethal doses is only 7-8 mL PQ [1], and no patient will survive with a plasma PQ concentration over 5000 ng/mL [2]. To date, PQ has caused death of numerous people in the world, which is higher than any other herbicidal agents [3]. For example, PQ leads to an estimated 300000 deaths in the Asia-Pacific region every year [4], [5]. There were 1741 suicides per 100, 000 documented from 1986 to 2005 in India [6]. Therefore, PQ has been banned in some countries such as South Korea and Europe. However, PQ is still widely used in many developing countries because of its effective quick-acting and non-selective weeding. Even in the United States, the use of PQ has increased four-fold in the past 10 years [7].

In order to reduce the mortality of PQ poisoning, the mechanism of intoxication has been studied intensively. PQ mainly affects the metabolism of NADPH-mediated cytochrome P450 reductase and xanthine oxidase. During the process, it produces a plenty of PQ mono-cation radical (PQ+), which

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is rapidly re-oxidized to PQ2+ and produces superoxide (O2−) [8]. The reactive oxygen will result in toxicity in human body such as liver, kidney and lung [9]. Based on the studies of mechanism of intoxication, the current therapeutic procedures mainly include the hemopurification of PQ, and the treatment of antioxidants [10], [11]. However, doctors must recognize the degree of intoxication before initiating treatments.

It has been confirmed that The PQ concentration (PQC) is related to the severity of PQ poisoning. Because PQC should be determined by high performance liquid chromatography (HPLC) or liquid chromatograph-mass spectrometer (LC-MS), it requires high precise and accurate equipment [12], [13]. Indeed, it is rarely used as a routine test in every hospital. The blood biochemical examination of hepatic and renal function is the most popular and common test in clinical practice. So far, the correlation of biochemical indexes of hepatic and renal function with prognosis of PQ poisoned patients is still unclear, and the significance of those biochemical indexes hasn't been investigated intensively.

As a new and efficient machine learning method, extreme learning machine (ELM) has its unique advantage such as its fast learning speed and excellent generalization. Besides, it can keep fewer fine-tuning parameters than the traditional artificial neural networks. Since its introduction, ELM has been applied in diagnosis of glaucoma and Parkinson disease [14], [15], no-reference assessment of image quality [16], human face recognition [17], and classification in remote sensing hyperspectral images [18].

In the previous paper [19], ELM has been demonstrated an effective and efficient prediction method for PQ diagnosis by using the blood metabolomics data. In this study, ELM is applied to explore the diagnostic value of biochemical indexes in prognosis of PQ poisoned patients.

II. MATERIALS AND METHODS

A. ETHICS STATEMENT

All of the process of experiments approved by the Medical Ethics Committee of First Affiliated Hospital of Wenzhou Medical University (Register number; 2016052), was carried out in accordance with the Declaration of Helsinki. The biochemical indexes of PQ poisoned patients hospitalized in emergency room of First Affiliated Hospital of Wenzhou Medical University from October 1st, 2013, to October 1st, 2017 were involved in this study.

B. DATA PREPARATION

A total of 101 PQ poisoned patients (male 56, female 45) were analyzed in this study. The average age was 33.74 ± 13.61 years, and the median age was 32 years. The initial plasma PQC and biochemical test were tested at the first time when the patients were hospitalized in EICU before they received any treatments. After the blood samples were collected, the PQ-poisoned patients had comprehensive treatment like hemoperfusion treatment with immunosuppressant drugs, liver-protective drugs and so on. According to the therapeutic outcome, they were assigned into survival group or dead group.

The plasma PQ concentrations were analyzed by the Agilent 1260 HPLC equipped with Agilent HC-C18 column (2.1 mm × 150 mm, 5 μm) and diode array Please refer to published articles for the detailed analytical information and validation information [20]. The biochemical test was determined by RA - 2000 automatic biochemical analyzer.

The detailed descriptions of 12 blood indexes were listed in Table 1. Before ELM modeling, the statistical analysis of the independent sample test was performed by using the software SPSS 17 (Table 2).

TABLE 1. List of the features used in this study and their definitions.

Number	Features	Abbreviation
F1	total bilirubin	TBIL
F2	direct bilirubin	DBIL
F3	indirect bilirubin	IBIL
F4	total protein	TP
F5	albumin	ALB
F6	albumin-globulin ratio	A/G
F7	alanine aminotransferase	ALT
F8	aspartate aminotransferase	AST
F9	the ratio of AST to ALT	ALT/AST
F10	blood glucose	GLU
F11	urea nitrogen	BUN
F12	creatinine	CR

TABLE 2. Statistical analysis of 101 PQ poisoned patients (dead group and survival group).

Index	Dead (n=51)	Survival (n=50)	p-value
TBIL	40.71±1.68	19.20±23.70	<0.001
DBIL	28.29±28.53	10.67±19.21	<0.001
IBIL	12.19±5.29	9.57±5.28	0.013
TP	64.49±6.24	64.83±6.01	0.778
ALB	37.88±4.53	38.13±4.35	0.769
A/G	1.44±0.24	1.45±0.26	0.891
ALT	164.79±176.68	64.82±110.91	0.001
AST	232.81±218.42	48.96±59.19	<0.001
ALT/AST	0.69±0.39	1.05±0.72	0.002
GLU	8.68±3.85	7.68±2.20	0.111
BUN	7.69±5.31	5.53±4.63	0.03
CR	167.71±115.86	95.02±109.59	0.001

C. ELM MODEL

The proposed ELM method provides an efficient method to distinguish the dead PQ poisoning patients from the survived people. The flowchart of the introduced ELM method was

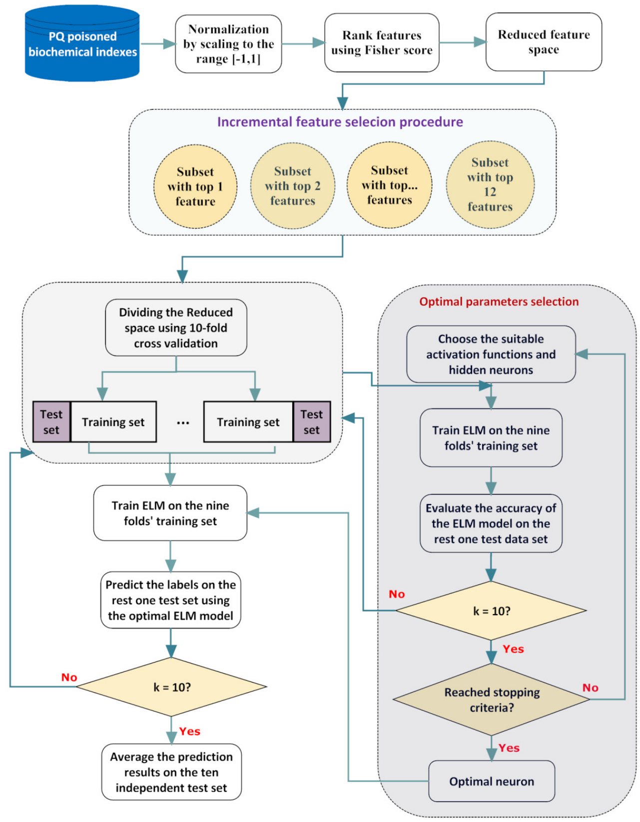

FIGURE 1. Flowchart of the proposed method.

shown in Figure 1. First, the important correlated indexes were screened by feature selection. Subsequently, ELM classifier was used to develop an optimal model with different feature sets. Finally, according to the best discriminating features, the predictive model developed and conducted the prognostic task in PQ poisoned patients.

1) FEATURE SELECTION

An efficient feature selection process is a crucial part of a machine learning method. It can eliminate the irrelevant and redundant variables in the data set. Therefore, feature selection can not only improve the accuracy of classifier models but also help better understand the underlying mechanism of the problem [21]. In this study, Fisher Score [22] feature selection is used to find the crucial features in biochemical indexes. Fisher Score employs the fisher criterion to recognize discriminative features. The score for each feature can be defined by the formula as follows. For the detailed information, please refer to published articles [23].

$$F = \frac{\sum_{i=1}^{2} n_i(\mu_i - \mu)^2}{\sum_{i=1}^{2} n_i(\sigma_i)^2}. \tag{1}$$

2) ELM CLASSIFICATION

According to the data sets obtained by Feature selection, an ELM model was developed for classification tasks. First, the activation functions and neuron number in hidden layer of ELM model were evaluated. When the optimal activation function and neuron in hidden layer were determined, ELM was used to predict the prognosis of PQ poisoning patients. A brief introduction of ELM was below. Please refer to the published works [24] for more information.

In a N samples training data set $\Re = \{x_i, t_i\}_{i=1}^{N}$, $x_i \in R^n$ meant the input variable with n features, and $t_i \in R^m$ meant the target variable with m dimensions. The output of ELM model was as follows [25]:

$$\sum_{i=1}^{k} \beta_i g(w_i \cdot x_j + b_i) = o_j,\ j = 1, 2, \ldots, N \tag{2}$$

where g(x) was activation function, k and β_i were neurons in hidden layer and the weight variable between the hidden neuron and the output layer. For more detailed information refer to published articles [23].

If an ELM model could contain zero error by approximating these N samples, we could get

$$\sum_{i=1}^{k} \beta_i g(w_i \cdot x_j + b_i) = t_j, \quad j = 1, 2, \ldots, N.$$

This equation could be reformulated as follows:

$$\mathrm{H}\beta = \mathrm{T} \tag{3}$$

where H [26] meant the hidden layer output matrix of the neural network:

$$\mathrm{H}=\begin{pmatrix} g(w_1 \cdot x_1 + b_1) & \ldots & g(w_k \cdot x_1 + b_k) \\ \vdots & \ddots & \vdots \\ g(w_1 \cdot x_N + b_1) & \cdots & g(w_k \cdot x_N + b_k) \end{pmatrix}_{N \times k} \tag{4}$$

$\beta = [\beta_1, \cdots, \beta_k]^T$ was the matrix of output weights, and $\mathrm{T} = [t_1, \cdots, t_N]^T$ indicated target labels' vectors. Since the Moor-Penrose (MP) can generalize inverse of matrix H, β can be listed as follows:

$$\beta = \mathrm{H}^{\dagger}\mathrm{T} \tag{5}$$

In summary, ELM algorithm included two steps: assigning randomly the input weights and bias and calculating the output matrix and weight of hidden layer.

3) EXPERIMENTS

To verify the developed ELM model for prognosis of the PQ poisoned patients, the support vector machines (SVM), probabilistic neural network (PNN) and back propagation neural network (BPNN) were employed for a comparison. The SVM model was developed by the LIBSVM toolbox [27]. The PNN and BPNN were developed by the algorithms implemented in MATLAB neural network toolbox. The ELM model was developed by coding at http://www3.ntu.edu.sg/home/egbhuang.

Before the classification, the biochemical data was normalized into the range $[-1, 1]$. The experiment was tested on an AMD FX(tm)$-$8350 Eight-Core Processor (4.0 GHz) running Windows 7.

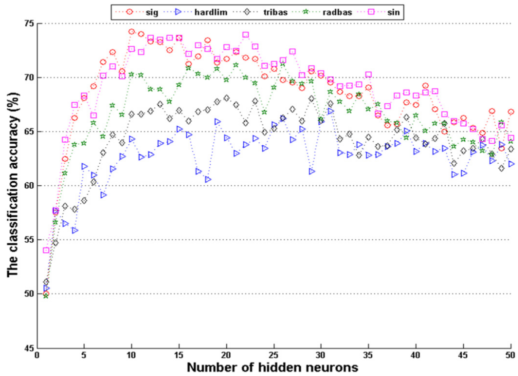

FIGURE 2. The relationship between ELM with different activation functions and the different number of hidden neurons.

The 10-fold CV [28] was used to evaluate classification performance. The final result was computed by averaging the results of all 10 trials. The proposed models were evaluated by parameters as follows:

$$ACC = \frac{TP + TN}{TP + FP + FN + TN} \times 100\% \tag{6}$$

$$Sensitivity = \frac{TP}{TP + FN} \times 100\% \tag{7}$$

$$Specificity = \frac{TN}{FP + TN} \times 100\% \tag{8}$$

TP and TN was the number of true positives and true negatives, which stood for the cases correctly predicted in dead or alive patients. FN and FP was the number of false negatives and false positives, which stood for the cases incorrectly predicted in dead or alive patients.

III. EXPERIMENTAL RESULTS

A. ELM CLASSIFICATION PERFORMANCE

The ELM performance is influenced by the activation functions and hidden neurons [29]. In this study, five activation functions including Sigmoid (sig), Sine, Hard-limit, Triangular basis and Radial basis function and the different number of neurons [1, 50] were evaluated in the prognosis of PQ poisoning patients. The results of classification accuracy of ELM were given in Figure 2. The sig function outperformed the others in the range of the first 10 hidden neurons, but its performance degraded with the increase of the neurons. In general, there was no function that dominated the other ones in the whole range of 1 to 50 neurons. In average, those five functions had the nearly same influence on the ELM model. It suggested that the ELM model was not very sensitive to the activation function involved in the problem we investigated. For convenience, we chose the sig activation function in the following experiments due to its better performance with a small amount of hidden neurons (1 to 10) than others.

As for the optimal neuron number in hidden layer, the classification performances of the different neurons in hidden layer were recorded and shown in Figure 3. ELM performed better with the smaller number of neurons than the bigger neurons, which was consistent with the phenomenon observed in the previous experiment. Table 3 listed the results of average classification performance in different numbers of hidden neurons (1, 5, 10, 15, 20, 25 and 30). The 10 hidden neurons achieved the highest validation performance with the ACC of 74.79%, sensitivity of 68.23% and specificity of 81.70%. The detailed results of the ELM with the best hidden neurons were listed in Table 4.

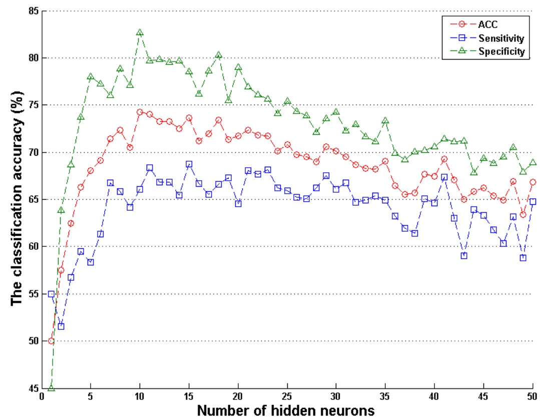

FIGURE 3. Average ACC, sensitivity and specificity versus different hidden neuron numbers for ELM via 10 runs of 10-fold CV.

TABLE 3. Average classification performance results of 10-fold CV.

Different number of hidden neurons	Average classification performance		
	ACC (%)	Sensitivity (%)	Specificity (%)
1	50.09 ± 0.47	60.00 ± 14.91	40.00 ± 14.91
5	67.11 ± 3.87	59.10 ± 5.51	75.50 ± 6.99
10	74.79 ± 2.93	68.23 ± 4.78	81.70 ± 2.89
15	72.86 ± 1.93	68.37 ± 2.72	77.70 ± 2.82
20	70.74 ± 2.20	67.03 ± 4.98	74.60 ± 2.93
25	72.29 ± 3.06	66.37 ± 3.72	78.40 ± 4.42
30	69.48 ± 2.71	64.80 ± 4.49	73.97 ± 3.77

B. COMPARISON WITH OTHER METHODS

The SVM, BPNN and PNN were conducted on the same dataset. For SVM, the parameter of RBF kernel function was determined by grid-search technique. The BPNN were tried in different numbers of nodes (2, 4, 6, 8 and 10) in the hidden layers with sig function and Levenberg-Marquardt algorithm. The best result was obtained at the learning epoch of 200 with 2 hidden nodes. These modeling parameter were used for the subsequent analysis. In order to determine the optimal spread of PNN, several values of the smoothing spread (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5) were tried to train PNN. The best

TABLE 4. The detailed results obtained by the ELM model with the best neurons.

Run	ACC (%)	Sensitivity (%)	Specificity (%)
1#	75.91	69.33	82.33
2#	77.55	73.33	82.00
3#	76.64	72.00	82.00
4#	72.82	67.67	78.33
5#	74.64	67.33	82.33
6#	73.73	62.00	86.33
7#	71.91	67.67	76.33
8#	80.00	75.67	84.67
9#	74.91	67.33	82.67
10#	69.82	60.00	80.00
Mean	74.79	68.23	81.70
Std.	2.93	4.78	2.89

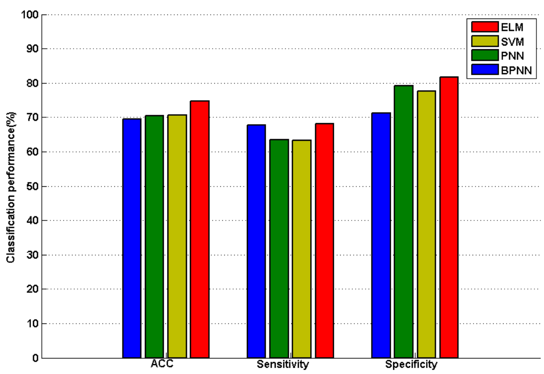

FIGURE 4. Comparison results of classification performance among ELM, SVM, PNN and BPNN.

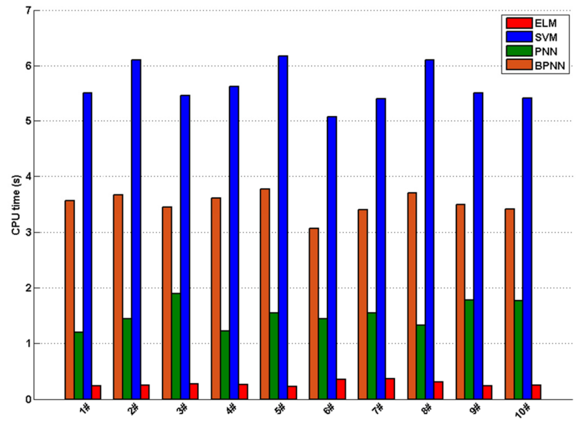

FIGURE 5. Computational cost comparison among ELM, SVM, PNN and BPNN.

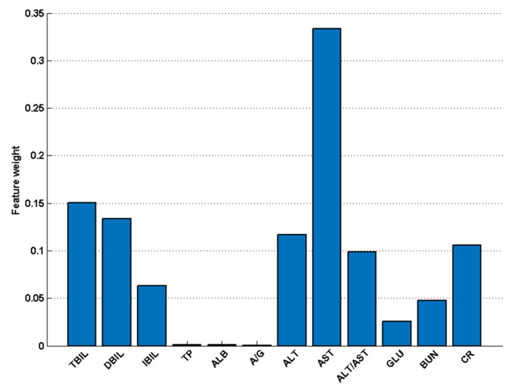

FIGURE 6. The importance of each index obtained by the Fisher Score feature selection.

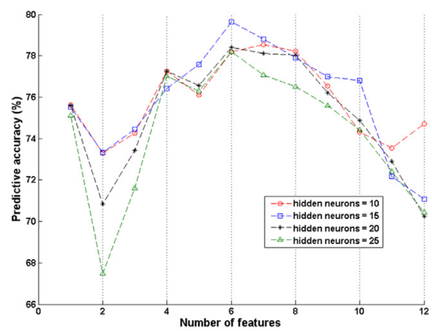

FIGURE 7. The incremental feature selection curve: the classification accuracy against the feature subset with different hidden neurons.

classification accuracy was obtained when the spread value was set to 5.

The classification performances of ELM, SVM, PNN and BPNN were showed in Figure 4. The comparison results of the CPU time of the four methods were displayed in Figure 5. From the two figures, it was clearly that ELM did not only perform the best among the four methods in terms of ACC, sensitivity and specificity, but also required the lowest computational demand among the four methods. The performance obtained by PNN was almost similar to that of SVM, but PNN required much less computational effort than that of SVM. Though BPNN achieved lower ACC and specificity than that of the other three methods, but its sensitivity was comparable to that of ELM. Among the four methods, SVM and BPNN consumed much more CPU resources than ELM and PNN. These results indicated that ELM had better generalization capabilities than other models by reducing the computational cost by 1 order of magnitude compared to other counterparts.

C. CLASSIFICATION WITH FEATURE SELECTION

The importance of each biochemical index was computed (Figure 6) and used to develop the optimal feature subset. According to importance, there were 12 different feature subsets developed from higher to lower rank and performed by ELM classifier. The incremental feature selection curve (in Figure 7) showed the models appeared a common trend,

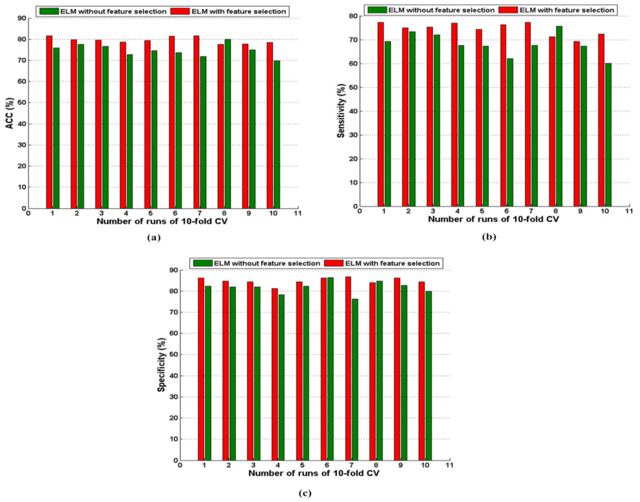

FIGURE 8. Comparison results of classification performance between ELM with and without feature selection.

TABLE 5. Paired t-test results of ELM with feature selection and without feature selection in terms of ACC, sensitivity and specificity.

Metrics	t-value (significance)
ACC	4.266 (0.002)
Sensitivity	3.534 (0.006)
Specificity	3.313 (0.009)

which indicated that the classification result was not very sensitive to the neuron number in hidden layer. The best classification result was an average of 79.6% ACC, 74.6% sensitivity, and 84.9% specificity for ELM when the dataset were comprised by top six features and the number of hidden neurons was 15. These six features were AST, TBIL, DBIL, ALT, CR and A/G. The comparison results of ELM with or without feature selection were shown in Figure 8. The classification accuracy of the best optimal data set was obviously superior to those of the whole feature set. These results indicated that the original data set contained redundant or irrelevant variable, which could be deleted by the Fisher Score feature selection.

The differences between the ELM with or without feature selection were analyzed by a paired t-test. It should be noted that the differences with $P < 0.05$ was considered to be statistically significant in the experiment. The results showed ELM with feature selection was better than ELM without feature selection (Table 5). The better performance revealed that Fisher score could select the most representative factors to construct the discriminative classifier.

The discriminative ability of the biochemical indexes was also compared with the ELM on the PQC data. In Figure 9, the optimal classification accuracy of ELM was in the 8 hidden neurons, and after then it performed relatively stable till the end with the ACC of 85.2%, sensitivity of 73.4% and

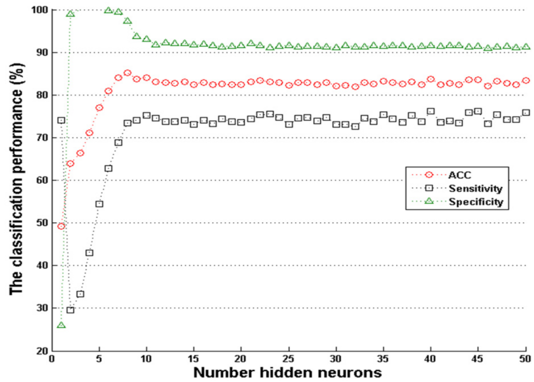

FIGURE 9. Average ACC, sensitivity and specificity versus different hidden neuron numbers for ELM via 10 runs of 10-fold CV on the data with PQC index.

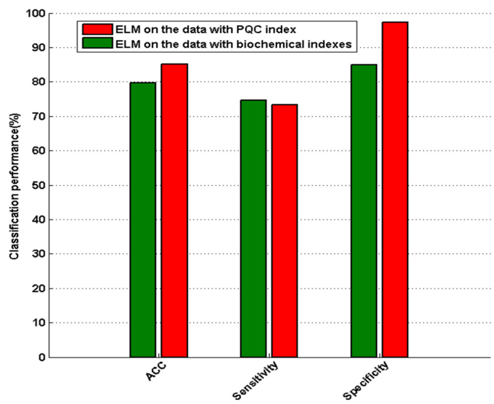

FIGURE 10. Comparison results of classification performance between ELM on the data with PQC index and biochemical indexes.

specificity of 97.2%. The comparison results of classification accuracy between ELM on the data with PQC index and biochemical indexes were given in Figure 10. From the figure, the results obtained by the biochemical indexes were comparable to that of PQC index.

IV. DISCUSSION AND FUTURE WORK

Biochemistry tests usually measure the chemical substances in the plasma to indicate the function of liver and kidney. Besides, it can indicate the levels of fat and glucose circulating in the body. The test of blood lipids in clinical field commonly include total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high-density lipoprotein (HDL). These indexes are usually used to assess the risk of atherosclerosis and subsequent risk of heart disease, but they haven't been tested in poisoning diseases. The liver and kidney function different from blood lipids can be destroyed in poisoning conditions. Therefore, they are tested in clinical practice routinely. However, there is no further comprehensive investigation to evaluate the relationship of biochemical indexes and poisoning degree in PQ poisoning patients, especially to discover which indexes is the most important one.

The problem of prognosis of PQ poisoning can be regarded as a problem of predicting the bad or dead status and well or alive status. It has the characteristics of multivariate and complex relationships. Therefore, ELM can be a good candidate as a classification method in this scenario [25]. For comparison purposes, the advanced SVM [30], PNN and BPNN, were also used to investigate the prognosis of PQ patients. In addition, Fisher Score selection was employed to identify correlating factors before the ELM classification models were constructed. The classification performance such as accuracy (ACC), sensitivity and specificity was examined.

According to the results of our proposed ELM machine learning approach, AST, TBIL, DBIL, ALT, CR and A/G were identified as the important factors for evaluation of poisoning degree. AST was the most important one among them. The Independent-Sample Test showed that their p-values were all below 0.005 which are much smaller than the other indexes such as BUN and IBIL. In other words, the results of the proposed ELM approach were consistent with statistical analysis. When the dataset was consisted with six indexes, the maximal classification accuracy reached up to 79.6%, which was nearly similar to the prediction accuracy of PQ plasma. It indicated that AST, TBIL, DBIL, ALT, CR and A/G could replace PQC to predict the prognosis of PQ poisoning. Therefore, doctors could use these biochemical indexes to directly predict the poisoning degree or prognosis of PQ-poisoned patients if they have no PQC data at hand. In addition, considering the speed of the proposed methodology, it is of significant importance to solve the problem of treatment of PQ poisoned patients. In fact, a timely decision can help doctors to make appropriate treatment protocols in time such as identifying the amount of hemoperfusion and the dosage of drugs.

So far, it is well known that the plasma level of PQ concentration is commonly recognized as the most important and sensitive index to predict the prognosis of PQ poisoning. Because the mortality rate and prognosis of PQ poisoning is highly correlated with blood PQ concentrations [31]. Our study has provided totally new reference to predicting the prognosis. The AST, TBIL, DBIL, ALT and A/G are vital hepatic indexes. AST and ALT are important enzymes in the liver, which play an important role in amino acid metabolism. AST and ALT are normally found less in the plasma. The increased level of AST and ALT in the blood often indicates the damage to the liver. CR is the most commonly used renal index. The increased level of CR is related to an actual kidney injury. Therefore, we can not only find out whether or not the liver and kidney have been destroyed, but also we can predict the poisoning degree or prognosis of PQ poisoning patients.

The early identification of poisoning degree and recognition of liver and kidney function of PQ poisoning patients is of great use in clinical practice. According to the results of our investigation, we have found out the most relevant indexes associated with the poisoning degree in blood biochemical test. The doctors should pay attention to these factors closely in clinical field, especially when there was no data of PQ plasma concentration available. And also, the doctors can make the treatment plan directly based on the level of AST, TBIL, DBIL, ALT, CR and A/G.

In brief, this study makes the following contributions: (1) a new method for prognosis of PQ poisoning patients by using biochemical indexes is proposed; (2) An ELM approach for automatically diagnosing the prognosis of PQ poisoning patients is developed; and (3) The most relevant biochemical indexes correlated with the dead status is selected by the Fisher score feature selection.

V. CONCLUSION

An effective data-driven ELM model based on the biochemical indexes has been successfully developed and applied to the practical PQ poisoning problem. AST, TBIL, DBIL, ALT, CR and A/G are the most critical indexes for the evaluation of poisoning degree. The maximal classification accuracy is 79.6%, when these six indexes are selected as the dataset. The biochemical test can be a viable alternative to predict the poisoning degree or prognosis of PQ poisoning, even if there was no available PQC measure.

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(Lufeng Hu and Panxin Yang contributed equally to this work.)

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LUFENG HU is currently an Associate Chief Pharmacist with the Department of Pharmacy, The First Affiliated Hospital, Wenzhou Medical University. His main research interests include therapeutic drug monitoring, poisoning detection, and pesticide toxicology.

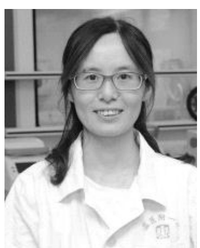
PANXIN YANG is currently pursuing the degree with the School of Laboratory Medicine and Life Sciences, Wenzhou Medical University. His main research interest includes medical diagnosis.

XIANQIN WANG is currently a Senior Experimentalist with the Analytical and Testing Center, Wenzhou Medical University, China. His main research interests include poisoning detection and pesticide toxicology.

FEIYAN LIN is currently an Experimentalist with the Central Laboratory, The First Affiliated Hospital, Wenzhou Medical University. Her main research interests include therapeutic drug monitoring, oncology, poisoning detection, and pesticide toxicology.

HUILING CHEN received the Ph.D. degree from the Department of Computer Science and Technology, Jilin University, China. He is currently an Associate Professor with the Department of Computer Science and Technology, Wenzhou University, China. He has published more than 100 papers in international journals and conference proceedings, including *Pattern Recognition*, *Expert Systems with Applications*, *Knowledge-Based Systems*, *Soft Computing*, *Neurocomputing*, and PAKDD. His present research interests include machine learning and data mining, and their applications to medical diagnosis and bankruptcy prediction. He is currently a Reviewer for the IEEE TRANSACTIONS ON SYSTEMS, MAN, AND CYBERNETICS, PART B.

HONGCUI CAO is currently a Senior Technician and a Doctoral Supervisor with the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, School of Medicine, Zhejiang University. Her main research interests include stem cells and liver regeneration and repair, poisoning detection, and pesticide toxicology.



HAIYING LI is currently a Clinical Laboratory Technician with the Central Laboratory, The First Affiliated Hospital, Wenzhou Medical University. Her main research interests include therapeutic drug monitoring, hematology, poisoning detection, and pesticide toxicology.