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Early Prediction of Acute Respiratory Distress Syndrome in Patients with Severe Trauma Based on Machine Learning

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Abstract: *An early prediction of Acute Respiratory Distress Syndrome (ARDS) in patients with severe trauma based on clinical data can help nurse clinicians screen high-risk groups that would develop ARDS. To achieve this purpose, machine learning methods were adopted and tested. This retrospective cohort study was performed on the data of the severe trauma patients admitted to the ICU of the affiliated hospital of Zunyi Medical University from September 2021 to November 2022. The required data for construing the prediction models was collected from medical records of these patients. Univariate logistic regression was used first to achieve the purpose of reducing the data dimension. Then, twelve machine learning methods classified into four categories, which were neural network, logistic regression (LR), decision tree (DT) and support vector machine (SVM), were adopted in the early prediction of ARDS in patients with severe trauma. Internal cross-validation was conducted in 50 numerical experiments, and in each test, a training set consisted of 80% of the samples that were randomly selected, and the remaining 20% of the samples were in a validation data set. In the internal validation, 550 patients were involved. 250 cases developed ARDS within one week and 300 cases had no ARDS. Machine learning methods were also tested in external validation with 100 trauma patients who developed ARDS within one week and 101 controls. Based on the test results, the optimal machine learning model was investigated. Then, significant predictors associated with the development of ARDS were further examined with the help of SHAP (SHapley Additive exPlanations) analysis and causal inference. Tree models showed high discrimination in both internal and external validation. The model trained by the AdaBoost + DT (decision tree) algorithm had the most balanced results, and showed that AUC (area under the curve), accuracy, precision, specificity and sensitivity were 0.915, 0.833, 0.799, 0.823, 0.845, respectively, in the cross validation, and 0.851, 0.751, 0.734, 0.710, 0.793, respectively, in the external validation. The findings indicated that Glasgow Coma Scale (GCS), Injury Severity Score (ISS), Total protein (TP), and blood glucose (Glu) were the most important relevant factors for the ARDS prediction. The use of collected clinical data to predict the development of ARDS in patients with severe trauma has a certain value. Tree models have the best discrimination power in predicting ARDS after major trauma. Essential predictors at least contain GCS, ISS, TP, and Glu.*

Keywords: *Severe Trauma, Acute Respiratory Distress Syndrome, Machine Learning*

1. Introduction

1.1 Background

Severe trauma (Injury Severity Score (ISS)≥16) is a leading cause of death among young people in both developed and developing countries, as a result of traffic accidents and work accidents[1, 2]. Acute injuries can cause secondary tissue damage due to the ischemia-reperfusion injury, as well as a systemic inflammatory response and extensive damage to pulmonary capillary endothelial cells and pulmonary epithelial cells, and eventually cause the development of Acute Respiratory Distress Syndrome (ARDS) [3, 4]. So, one of the most common secondary diseases of severe trauma is ARDS. The statistics showed that the prevalence of traumatic ARDS ranged between 25% and 50% [5, 6], and the incidence of ARDS was approximately 10.4% in patients in the intensive care unit (ICU), where traumatic patients account for 6.5% [7, 8]. Severe trauma patients with ARDS also have a high mortality rate, with a nearly 40% chance of dying [8, 9]. Early identification of high-risk patient groups of ARDS

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after severe trauma is critical for timely supportive treatment and nursing, and it can help reduce the incidence of the development of ARDS and further improve the medical prognosis of trauma patients.

1.2 Related works

Currently, risk factors for the development of ARDS in trauma patients have been studied extensively, but only a few works involve the early prediction of ARDS in trauma patients.

Investigations of risk factors for the development of ARDS in trauma patients could be found in the literature [6, 9-26]. In [9-12], risk factors for ARDS after trauma were studied in patients with different injury mechanisms. In [6, 20-21], the problem of determining risk factors for ARDS was mainly discussed in patients with multiple injuries. In [15-16], associations between the development of ARDS in trauma patients and the two risk factors, sex and acute blood transfusion, were surveyed. Mortality in trauma patients complicated with ARDS and its relevant factors were also studied in [24-29]. Based on the literature review, it was found that risk factors for ARDS after severe trauma included APACHE(Acute Physiology and Chronic Health Evaluation)-II score, ISS, Glasgow Coma Scale (GCS), massive transfusion, sex, admission hypotension, infection, pneumonia, pulmonary contusion, flail chest injury, age, admission tachycardia, history of cardiopulmonary and hematologic disease, preexisting vascular and respiratory diseases, surgical operation, blood glucose, chronic alcohol use, diabetes mellitus, smoking, sepsis, use of total parenteral nutrition, shock, gastrointestinal hemorrhage, disseminated intravascular coagulation, etc. The validation of biomarkers in the diagnosis and prediction of ARDS in trauma patients was also investigated in [13].

To obtain an early clinical prediction result for the development of ARDS in trauma patients based on risk factors, multivariate logistic regression had been adopted [20, 22]. However, far few studies discussed modern machine learning algorithms in the prediction of ARDS after trauma. Some works discussed the prediction of ARDS in critical patients using machine learning algorithms [30-31], but did not focus on trauma patients. Various intelligent machine learning algorithms were used to assist in the prediction of ARDS based on clinical records and biological examinations in patients with diseases such as Corona Virus Disease 2019 (COVID-19) and severe acute pancreatitis [32-34]. To the authors' knowledge, only one ARDS prediction study based on modern machine learning technology could be found in patients after severe trauma [35]. In this work, deep learning-based image processing technology was adopted, and this work did not cover specific clinical records and biological examinations. An early prediction model of ARDS in patients with severe trauma based on clinical records and biological examinations is an important aid to the diagnosis that relies only on imaging examinations. And this was the main research objective of this paper.

1.3 Researches in this study

Machine learning technology can be used to analyze known information comprehensively, and due to the introduction of a penalty function with regularization, many machine learning algorithms can effectively reduce the influence of collinearity. Therefore, machine learning algorithms are powerful technical means for data analysis and the prediction of clinical outcomes [36]. The predictability of ARDS in trauma patients can be observed in machine learning models, and the impacts of different relevant factors on prediction results can also be explored further. In this research, four categories of machine learning methods, neural network, logistic regression (LR), decision tree (DT), and support vector machine (SVM), were adopted to predict whether patients with severe trauma would develop ARDS within one week after admission to the hospital. These methods included random forest (RF), AdaBoost + DT, Gradient Boosting Decision Tree (GBDT), eXtreme Gradient Boosting (XGBoost), LR, Bagging + LR, AdaBoost + LR, SVM, Bagging + SVM, AdaBoost + SVM, multilayer perception (MLP), and Bagging + MLP, specifically [37-38]. Subsequently, the associations between predictors and ARDS in trauma patients were further discussed based on SHAP (SHapley Additive exPlanations) analysis [39] and causal inference [40, 41].

2. Materials and Methods

2.1 Study design

Potential predictors from the literature and expert opinions, and also with clinical accessibility, were comprehensively considered and collected. Patients were eligible if they were at least 18 years old,

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were admitted to the hospital within 24 hours after trauma and had

Table 1 Clinical data collected from severe trauma patients

Indicators	Not ARDS(n=300)	ARDS(n=250)	*P*-value
General information			
Age (year)	49(39, 57)	53(46, 57)	0.001
Male sex	217(72.30%)	198(79.20%)	0.062
Smoking			
No	210(70.00%)	146(58.40%)	0.005
Yes	90(30.00%)	104(41.6%)	
Drinking			0.035
No	216(72.00%)	159(63.60%)	
Yes	84(28.00%)	91(36.40%)	
Injury mechanism			0.421
Traffic accident	138(46.00%)	114(45.60%)	
Fall	74(24.67%)	66(26.40%)	
Other	88(29.33%)	70(28.00%)	
Consultation time window after trauma (CTWAT) (hour)	5(3, 7)	5(3, 8)	0.642
Systolic blood pressure (SBP) (mmhg)	122.00(109.50, 137.00)	117.00(97.00, 128.00)	<0.001
Diastolic blood pressure (DBP) (mmhg)	77.00(69.00, 85.00)	72.0(63.00, 81.00)	<0.001
Heart rate (times/min)	87.00(78.00, 98.00)	90.00(80.00, 105.00)	0.004
Respiratory rate (times/min)	20(19, 21)	20(19, 22)	0.010
Laboratory examinations			
Oxygen saturation (SaO2) (%)	98(97, 98)	98(96, 98)	0.310
White blood cell count (WBC) (109/L)	13.78(11.00, 18.29)	15.76(12.03, 19.74)	0.003
Granulocyte (Gran) (109/L)	12.07(8.88, 16.15)	12.94(10.35, 17.13)	0.006
Prothrombin time (PT) (s)	10.70(9.85, 12.10)	11.00(10.40, 12.70)	<0.001
Activated partial thromboplastin time (APTT) (s)	26.15(23.65, 30.40)	25.30(23.70, 29.35)	0.347
Fibrinogen (FIB) (g/L)	2.37(1.90, 2.90)	2.13(1.64, 2.60)	<0.001
Hematocrit (HCT) (%)	39(34, 42)	36(31, 40)	<0.001(0.232)
Platelet (PLT)	201.37±68.71	188.17±68.19	0.035
Blood potassium (mmol/L)	3.80(3.53, 4.11)	3.90(3.58, 4.23)	0.073
Blood sodium (mmol/L)	139.04(137.80, 140.93)	140.32(138.72, 142.00)	<0.001
Cholinesterase (ChE) (K/uL)	7.0(5.8, 8.3)	6.4(4.9, 7.3)	<0.001(0.204)
Total protein (TP) (g/L)	61.50(56.46, 66.15)	56.31(49.30, 62.00)	<0.001
Albumin (ALB) (g/L)	38.10(34.80, 41.00)	35.20(30.90, 39.10)	<0.001(0.633)
Prealbumin (PA) (mg/L)	216.5±58.4	204.0±54.2	0.010
Serum creatinine (SCR) (μmol/L)	70.00(60.50, 82.50)	75.50(63.00,89.00)	0.002
Serum bicarbonate (HCO3) (mmol/L)	20.98±3.36	20.83±3.28	0.584
Blood glucose (Glu) (mmol/L)	7.07(6.05, 8.20)	8.28(6.90, 10.26)	<0.001
Creatine kinase (CK) (U/L)	449.00(231.00, 890.00)	621.98(232.74, 1587.54)	0.001
Creatine kinase isoenzyme MB (CK-MB) (U/L)	32(19, 49)	41(25, 67)	0.001(0.347)
Treatments			
Blood transfusion			<0.001
No	192(64.00%)	116(46.40%)	
Yes	108(36.00%)	134(53.60%)	
Emergency operation			0.005
No	202(67.33%)	137(54.80%)	
Yes	98(32.67%)	113(45.20%)	
Underlying diseases			
Hypertension			0.269
No	276(92.00%)	236(94.40%)	
Yes	24(8.00%)	14(5.60%)	

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Table 1 Continued

Indicators	Not ARDS(n=300)	ARDS(n=250)	*P*-value
Diabetes mellitus			0.534
No	286(95.30%)	241(96.40%)	
Yes	14(4.70%)	9(3.6%)	
Initial CT scans			
Acute lung injury			<0.001
No	149(49.67%)	72(28.80%)	
A single side	15(5.00%)	41(14.40%)	
Both sides	136(45.33%)	137(54.80%)	
Pneumohemothorax (Pne-thorax)			<0.001
No	236(78.67%)	198(79.20%)	
A single side	29(9.67%)	46(18.40%)	
Both sides	35(11.67%)	6(2.40%)	
Disease severity			
Abbreviated Injury Score (AIS)			
AIS - Head/Neck	0(0, 3)	0(0, 2)	0.785
AIS-APC (abdomen and pelvic cavity)	0(0, 2)	0(2, 3)	<0.001
AIS- Thorax	4(3, 4)	4(3, 4)	0.004
AIS - Extremities	2(0, 3)	2(1, 2)	0.750
AIS -Body surface	1(0, 1)	1(0, 1)	0.352
AIS- Face	0(0, 1)	0(0, 0)	0.048
ISS	24(20, 27)	29(24, 32)	<0.001
GCS	15(15, 15)	14(12, 15)	<0.001
APACHE-II Score	6(4, 8)	8(6, 11)	<0.001
Shock			<0.001
No	267(89.00%)	170(68.00%)	
Yes	33(11.00%)	80(32.00%)	

An ISS score of at least 16, as well as stayed in the hospital at least 72 hours. Patients who had incomplete clinical data, patients with ARDS at admission, patients with chronic obstructive pulmonary disease and chronic heart failure, patients with a stay of less than 24 hours and patients who died before developing ARDS were excluded from the study.

The primary dataset for this retrospective cohort study included 550 patients with severe traumatic injuries. 250 patients developed ARDS within one week after admission to the hospital, and 300 patients did not develop ARDS. All patients were from the affiliated hospital of Zunyi Medical University from September 2021 to April 2022. The diagnosis of ARDS was according to the Berlin definition [42]. Table 1 details the indicators of these patients.

A total of 100 trauma patients who developed ARDS within one week and 101 controls who did not develop Ards were included additionally in the external validation dataset. These cases were collected from July 2022 to December 2022, and also from the affiliated hospital of Zunyi Medical University.

2.2 Machine learning Models

Algorithms including RF, AdaBoost + DT, GBDT, XGBoost, LR, Bagging + LR, AdaBoost + LR, SVM, Bagging + SVM, AdaBoost + SVM, Multilayer Perception (MLP) and Bagging + MLP were adopted. In this study, the base classifier of the ensemble algorithms of GBDT, RF, and XGBoost was DT. Machine learning models were performed using the numerical simulation tool, Python (version 3.8.1) + Scikit-learn (version 1.1.3).

To evaluate the overall performance of prediction models, the prediction accuracy and AUC values were first considered, and then precisions, specificities and sensitivities were observed. AUC value (area under the curve) is the area under the Receiver Operating Characteristic (ROC) curve, and the following equations are the definitions of accuracy, precision, sensitivity and specificity.

$$\text{Accuracy}=(tp+tn)/(tp+fp+tn+fn) \tag{1}$$

$$\text{Precision}=(tp)/(tp+fp) \tag{2}$$

$$\text{Sensitivity}=(tp)/(tp+fn) \tag{3}$$

$$\text{Specificity}=(tn)/(tn+fp) \tag{4}$$

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Where, tp represents the number of actual positive cases that are predicted as positive results; tn represents the number of actually negative cases that are predicted as negative results; fn represents the number of actually positive cases that are predicted as negative results; and fp represents the number of actually negative cases that are predicted as positive results.

2.3 Data processing procedures

Theoretically, if there are sufficient samples, in machine learning methods, the influences and weights of irrelevant and low correlation factors can be lowered automatically. However, in view of the fact that the sample size is often limited, reducing the data dimension is necessary to reduce the impact of overfitting. Univariate logistic regression analysis was first used to select valuable variables. The variables that had a statistically significant relationship with the outcome “ARDS occurred during the observation period” were the selected variables.

The next step is the construction and validation of the ARDS prediction models. The test results of different prediction models were compared. Variable roles were also analyzed based on SHAP analysis and casual inference.

Details of data processing are shown in the steps detailed below and in Figure 1.

Step 1: This was a data collection and collation step. As most of the missing data in this study were missing observations of some continuous attributes, mean and mode values were preferentially used to fill in the missing pieces. For common physical signs, such as body temperature and arteria ph, the missing pieces were normal values by default.

Step 2: Univariate logistic regression was used to select valuable variables in this step. The outcome ‘ARDS occurred during the observation period’ was represented by 1, and ‘ARDS did not occur during the observation period’ was represented by 0. The collected indicators that were not significantly related to ARDS were not considered.

Step 3: In this step, the data transformation was implemented. Category variables were converted to binary codes. Continuous variables and rank variables were normalized as follow:

$$x_i = (x_i - x_{\min}) / (x_{\max} - x_{\min}) \tag{5}$$

Step 4: This step is model constructing. In addition to basic classifiers, some ensemble algorithms, such as AdaBoost, Bagging, GBDT, RF, and XGBoost were supplemented in this step. The holdout cross-validation was used in internal validation, and external validation was also conducted.

Internal cross-validation was conducted in 50 numerical experiments. And in each test, 80% of the samples that were randomly selected were placed in a training set, and the remaining 20% of the samples were in a validation data set. In external validation, all the 550 samples used in internal validation were used to train a model, and 201 samples in the external validation dataset were used as validation data. The performance of different machine learning algorithms was also compared and evaluated in this step.

Step 5: contributions of different predictors were compared using shap analysis. Important predictors for the development of ards in patients with severe trauma were analyzed on the basis of variable contributions. Casual inference was also adopted to analyze the predictor roles supplementary.

The general outline of the above steps is shown in Figure 1.

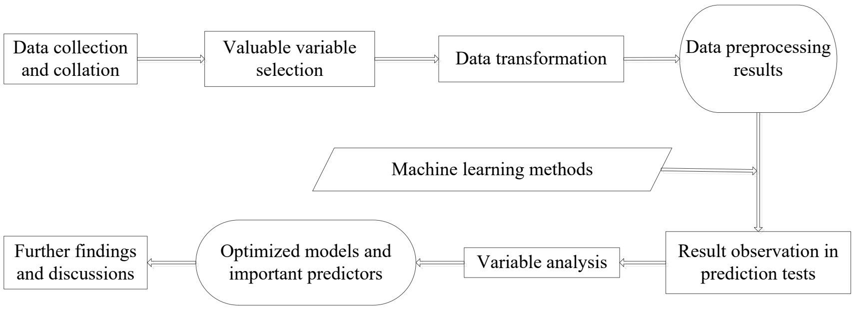

Figure 1 Data processing procedures in this paper

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2.4 Statistical analysis

The statistical analysis was performed using SPSS (version 19.0). The level of statistical significance was set at P<0.05. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. To compare the studied variables between the ARDS group and the non-ARDS group, the independent t-test was used in the case of normality and the Mann-Whitney U test was used in the case of non-normality. For qualitative variables, the Chi-square test or the Fisher test was used.

Causal inference tests were performed with the help of Python (version 3.8.1) + Microsoft DoWhy (version 0.8). In causal inference, three methods, the back-door criterion, the front-door criterion, and the instrumental variable analysis, were adopted in causal identifications. The ATE (Average Treatment Effect) value was used to evaluate the treatment effect.

3. Results

3.1 Valuable variable selection

The results of the variable selection using univariate logistic regression are shown in Table 2. Variables marked with '*' were selected variables. Table 2 indicates that, except for a few cases, most variables with significant difference between the two groups of patients also had significant impacts on the development of ARDS. Only variables, including HCT, ChE, CK-MB and ALB, had no significant correlations. These four variables were evaluated using the Mann-Whitney test in the base-line data. To further reduce the data dimension, MAP (mean arterial pressure) was used to integrate the information from SBP and DBP, and MAP= (2*DBP+SBP)/3.

Table 2 Inclusion variables in the ARDS prediction

Variables	Odd ratio	95%CI	*P*-value	Variables	Odd ratio	95%CI	*P*-value
Age*	1.019	1.007-1.030	0.002	AIS-Thorax*	1.160	1.021-1.319	0.023
Smoking*	1.662	1.168-2.364	0.005	AIS-APC *	1.326	1.189-1.479	<0.001
Drinking*	1.472	1.026-2.110	0.036	ISS*	1.112	1.081-1.144	<0.001
SBP*	0.982	0.973-0.990	<0.001	GCS*	0.736	0.667-0.812	<0.001
DBP*	0.974	0.961-0.987	<0.001	APACHE-II score*	1.141	1.094-1.190	<0.001
Respiratory rate*	1.067	1.007-1.131	0.029	Sex	0.687	0.462-1.021	0.063
Heart rate*	1.012	1.002-1.023	0.020	Injury mechanism	0.989	0.799-1.224	0.526
WBC*	1.041	1.012-1.070	0.004	CTWAT	0.976	0.951-1.001	0.065
Gran*	1.044	1.013-1.075	0.005	SaO2	0.947	0.890-1.008	0.087
PT*	1.156	1.060-1.261	0.001	APTT	1.007	0.994-1.019	0.285
FIB*	0.632	0.511-0.780	<0.001	HCT	0.600	0.245-1.472	0.265
PLT*	0.996	0.994-0.999	0.010	Blood potassium	0.981	0.868-1.110	0.762
Blood sodium*	1.136	1.068-1.208	<0.001	ChE	0.971	0.917-1.029	0.319
TP*	0.940	0.921-0.959	<0.001	HCO3	0.986	0.937-1.037	0.583
PA*	0.996	0.993-0.999	0.010	CK-MB	1.101	0.999-1.004	0.387
SCR*	1.010	1.003-1.018	0.006	Hypertension	0.682	0.345-1.349	0.272
Glu*	1.201	1.121-1.287	<0.001	Diabetes mellitus	0.763	0.325-1.793	0.535
CK*	1.001	1.000-1001	0.001	AIS - Head/Neck	0.987	0.880-1.108	0.827
Shock*	3.807	2.342-5.964	<0.001	AIS - Extremities	0.984	0.843-1.147	0.835
Blood transfusion*	2.054	1.458-2.893	<0.001	AIS -Body surface	0.900	0.700-1.158	0.412
Emergency operation*	1.075	0.747-1.548	0.006	AIS -Face	0.889	0.748-1.055	0.178
Acute lung injury*	1.143	1.179-1.694	<0.001	ALB	1.001	0.996-1.006	0.640
Pne-thorax*	1.429	1.099-1.858	0.008				

3.2 Performances of machine learning models

The parameters of the machine learning algorithms in numerical tests are shown in Table 3. And the performance of different machine learning models both in internal and external validation is shown in Table 4. In Table 4, the external validation results are also the average values in 50 numerical experiments. Prediction models with a standard deviation of 0.000 in the external validation were the stable ones.

The results in Table 4 show that tree models outperform other models. Accuracy, precision, sensitivity and specificity could reach 0.833, 0.829, 0.853, and 0.877 respectively. In general, the AdaBoost + DT model provided the best results. Compared to the GBDT model, the sensitivity value obtained by the AdaBoost + DT model is greater than the specificity value. Therefore, AdaBoost + DT was more capable of screening patients who would develop ARDS. It was also found that ensemble learning is more adapted to tree models, and ensemble algorithms in LR, SVM and neutral network had

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no advantages and sometimes even performed worse.

Table 3 Parameter choices in machine learning models

Methods	Parameters
RF	n_estimators: 120, criterion: 'entropy', max_depth: 9, min_samples_leaf: 3.
AdaBoost+DT	n_estimators: 120, algorithm: SAMME, max_depth: 9, min_samples_leaf: 3.
GBDT	n_estimators: 120, max_depth: 9, min_samples_leaf: 3, learning_rate: 0.1.
XGBoost	base_score: 0.5, booster: 'gbtree', colsample_bylevel: 1, colsample_bynode:1, colsample_bytree:1, gamma: 0, learning_rate: 0.1, max_depth: 9, min_child_weight: 1, n_estimators: 200, objective: 'binary:logistic', scale_pos_weight: 1.
LR	penalty: l2, tol: 1e-3, C: 1.0, solver: 'liblinear', max_iter: 10000.
Bagging+LR	n_estimators: 120, penalty: l2, tol: 1e-3, C: 1.0, solver: 'liblinear', max_iter: 10000.
AdaBoost+LR	n_estimators: 120, algorithm: 'SAMME.R', learning_rate: 0.1, penalty: l2, tol: 1e-3, C: 1.0, solver: liblinear, max_iter: 10000.
SVM	C: 1.0, gamma: 'auto', kernel: 'linear', tol: 1e-3, probability: 'True'.
Bagging+SVM	n_estimators: 120, C: 1.0, gamma: 'auto', kernel: 'linear', tol: 1e-3, probability: 'True'.
AdaBoost+SVM	n_estimators: 120, algorithm: 'SAMME.R', learning_rate: 0.1, gamma: 'auto', kernel: 'linear', tol: 1e-3, probability: 'True'.
MLP(1 hidden layer)	activation: 'logistic', solver: 'adam', alpha: 1e-2, hidden_layer_sizes: 9, learning_rate: 'constant', max_iter: 200000.
Bagging+MLP	n_estimators: 100, activation: 'logistic', solver: 'adam', alpha: 1e-2, hidden_layer_sizes: 9, learning_rate: 'constant', max_iter: 200000.

3.3 Variables in the prediction model

The SHAP method was adopted to analyze the contributions of different variables in prediction models. Figure 2 shows the influences of the predictors on the prediction outcomes in the AdaBoost + DT model. In the figure, the lengths of the bars indicate the SHAP values, which represent the correlations between the predictors and the development of ARDS.

To aid in the analysis of variable roles, causal inference results were also provided. A causal model is given in Figure 3. This causal model was proposed based on the assumption that each predictor had a path reaching the ARDS outcome, and also based on correlation information of variables from the literature know so far.

Table 5 and Figure 4 show the ATE results of different predictors according to the causal model. In Table 5, the P values indicate the differences between the ATE results in causal identifications and in refutation tests. The refutation tests were conducted using 'bootstrap validation' and 'random common cause validation' [43]. As each predictor had a pathway that led to the ARDS, mainly the back-door criterion was used in causal identification.

The smaller the ATE value of a variable is, the more likely this variable is a factor with spurious correlation. Tests based on variables with selected SHAP values and ATE values were provided to further investigate the importance of variables. And Table 6 shows the results.

Table 6 indicates that, on the whole, the models with more variables had better performance. However, comparable results could also be obtained even if some variables with lower SHAP values and lower ATE values were excluded. To improve the prediction performance, besides the most prominent predictors of GCS, ISS, TP, and Glu, secondary variables also played roles.

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Table 4 Performances of different machine learning methods

Validation Mode	Methods		AUC	Accuracy	Precision	Specificity	Sensitivity
Internal validation	DT	RF	0.887±0.030	0.797±0.033	0.762±0.058	0.791±0.052	0.807±0.054
		AdaBoost+DT	0.915±0.026	0.833±0.036	0.799±0.060	0.823±0.055	0.845±0.049
		GBDT	0.896±0.030	0.803±0.038	0.829±0.057	0.877±0.043	0.717±0.068
		XGBoost	0.888±0.032	0.809±0.037	0.775±0.059	0.801±0.056	0.820±0.060
	LR	LR	0.803±0.041	0.731±0.073	0.737±0.073	0.808±0.056	0.641±0.058
		Bagging+LR	0.803±0.041	0.728±0.040	0.733±0.070	0.805±0.055	0.639±0.056
		AdaBoost+LR	0.782±0.042	0.711±0.040	0.726±0.066	0.815±0.046	0.598±0.058
	SVM	SVM	0.819±0.040	0.752±0.040	0.747±0.065	0.806±0.050	0.688±0.056
		Bagging+SVM	0.817±0.041	0.739±0.043	0.750±0.072	0.822±0.052	0.641±0.059
		AdaBoost+SVM	0.794±0.041	0.699±0.041	0.738±0.073	0.840±0.054	0.535±0.076
	Neural Network	MLP	0.796±0.038	0.722±0.038	0.716±0.061	0.785±0.050	0.640±0.061
		Bagging+MLP	0.801±0.038	0.724±0.039	0.720±0.063	0.783±0.054	0.655±0.061
External validation	DT	RF	0.812±0.005	0.725±0.008	0713±0.018	0.691±0.012	0.758±0.012
		AdaBoost+DT	0.851±0.008	0.751±0.014	0.734±0.013	0.710±0.017	0.793±0.019
		GBDT	0.839±0.006	0.745±0.013	0.776±0.017	0.798±0.020	0.693±0.021
		XGBoost	0.815±0.000	0.746±0.000	0.736±0.000	0.720±0.000	0.772±0.000
	LR	LR	0.662±0.000	0.652±0.000	0.648±0.000	0.630±0.000	0.673±0.000
		Bagging+LR	0.661±0.003	0.652±0.006	0.648±0.007	0.630±0.006	0.673±0.006
		AdaBoost+LR	0.641±0.000	0.592±0.000	0.592±0.000	0.580±0.000	0.604±0.000
	SVM	SVM	0.668±0.000	0.657±0.000	0.640±0.000	0.590±0.000	0.723±0.000
		Bagging+SVM	0.673±0.005	0.640±0.008	0.631±0.008	0.594±0.011	0.686±0.012
		AdaBoost+SVM	0.642±0.007	0.601±0.010	0.587±0.009	0.504±0.025	0.698±0.020
	Neural Network	MLP	0.680±0.006	0.662±0.010	0.643±0.009	0.590±0.012	0.733±0.011
		Bagging+MLP	0.674±0.008	0.635±0.012	0.630±0.012	0.570±0.022	0.718±0.010

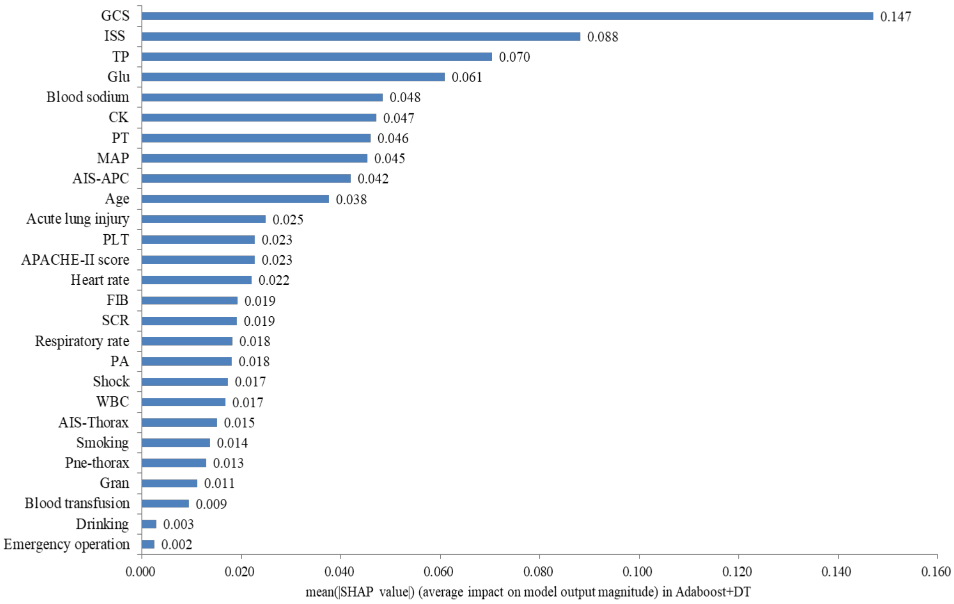

Figure 2 SHAP values in the Adaboost + DT model

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Table 5 Causal inference results

Variables	ATE in causal inference	ATE in bootstrap validation (0) /ATE after adding a common cause (1)	*P*-value (0) /*P*-value (1)
Age	0.2109	0.2004/0.2110	0.92/0.94
Smoking	0.1322	0.1334/0.1325	0.84/0.84
Drinking	0.0355	0.0423/0.0352	0.86/0.98
MAP	-0.1789	-0.1796/-0.1791	≈1.00/0.98
Respiratory rate	0.0356	0.0311/0.0351	0.96/0.84
Heart rate	-0.1766	-0.1917/-0.1778	0.94/0.96
WBC	0.3531	0.3393/0.3531	0.92/0.94
GRAN	0.1341	0.1489/0.1356	0.96/0.86
PT	-0.0218	-0.0208/-0..0202	≈1.00/0.92
FIB	-0.2005	-1.1893/-0.2003	0.94/0.80
PLT	-0.0175	-0.0376/-0.0188	0.94/0.86
Blood sodium	0.1494	0.1870/0.1487	0.82/0/98
TP	-0.3659	-0.3731/-0.3673	0.88/0.94
PA	-0.1099	-0.0928/-0.1089	0.94/0.96
SCR	-0.0417	-0.0241/-0.0418	0.78/0.94
Glu	0.4272	0.4002/0.4276	0.90/0.86
CK	0.1734	0.1927/0.1731	0.92/0.96
Shock	0.2716	0.2828/0.2716	0.86/0.92
Blood transfusion	0.1094	0.1044/0.1090	0.88/0.84
Emergency operation	0.0306	0.0322/0.0305	0.98/0.90
Acute lung injury	0.1158	0.1202/0.1159	0.96/0.90
Pne-thorax	0.1362	0.1287/0.1361	0.90/0.86
AIS-Thorax	0.1738	0.1662/0.1739	0.90/0.98
AIS -APC	0.2661	0.2506/0.2663	0.80/0.90
ISS	0.3105	0.3113/0.3110	0.96/0.88
GCS	-0.4335	-0.4260/-0.4334	0.92/0.96
APACHE-II score	0.1040	0.1011/0.1036	0.90/0.98

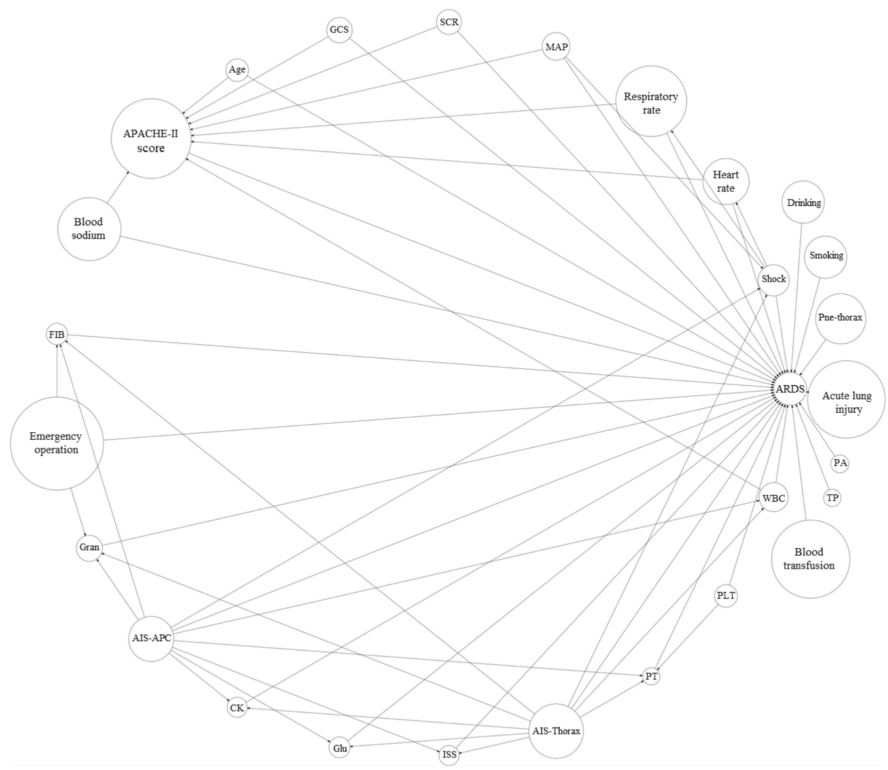

Figure 3 Diagram illustrating the causal model

4. Discussion

The Mann-Whitney U test is a nonparametric mean value test method. In this method only rank information is considered [44], and the characteristics of the variables were not fully investigated. So, in data preprocessing, univariate logistic regression was considered to have greater test power in identifying relevant factors. The four variables, HCT, ChE, CK-MB and ALB, were not included in the

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prediction models, although these variables had significant differences between patients with ARDS and patients without ARDS. In fact, if the requirement of normality was relaxed and it was assumed that natural variables with large samples will approximately be normal populations, P values for HCT, ChE, CK-MB and ALB would be 0.232, 0.204, 0.347, and 0.633, respectively, using the t-test.

In clinical and epidemiological studies, the sample size is calculated according to the parameters of the variables, such as the odds ratio, the probability of the baseline, the confidence lever, the significance level, etc., and the statistic power can also be calculated with given formulas.

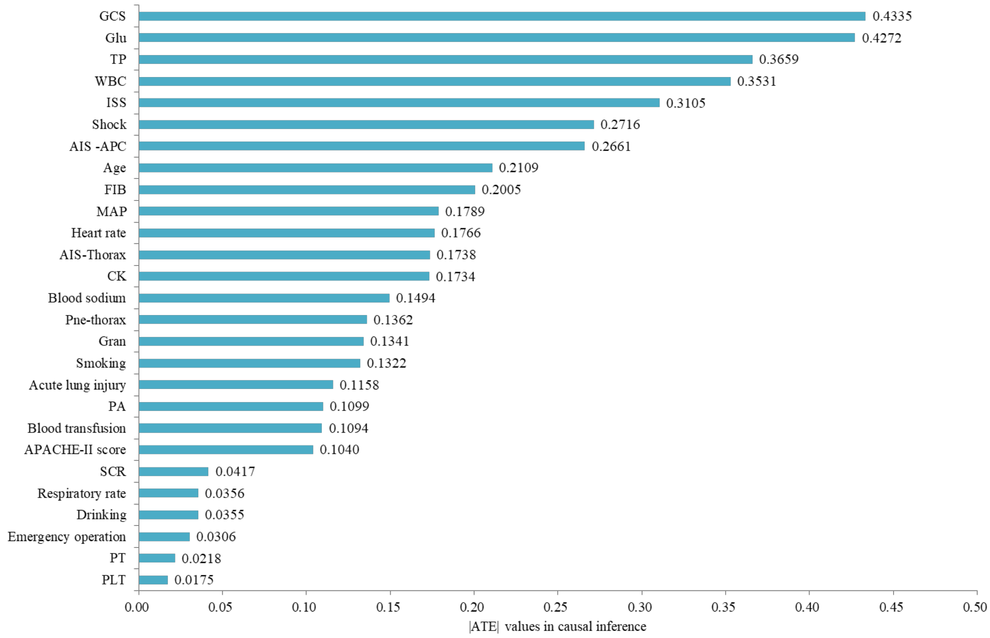

Figure 4 ATE values in causal inference

Table 6 Performances of the Adaboost+DT model with selected variables

Validation Mode	Methods	AUC	Accuracy	Precision	Specificity	Sensitivity
Internal validation	AdaTree-27 variables	0.915±0.026	0.833±0.036	0.799±0.060	0.823±0.055	0.845±0.049
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.015)	0.896±0.032	0.815±0.034	0.778±0.056	0.801±0.054	0.832±0.051
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.020)	0.885±0.033	0.797±0.034	0.766±0.057	0.796±0.051	0.799±0.058
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.040)	0.872±0.034	0.787±0.042	0.753±0.068	0.782±0.063	0.796±0.062
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.050)	0.830±0.038	0.762±0.037	0.730±0.065	0.770±0.056	0.755±0.059
External validation	AdaTree-27 variables	0.851±0.008	0.751±0.014	0.734±0.013	0.710±0.017	0.793±0.019
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.015)	0.843±0.008	0.754±0.014	0.737±0.013	0.715±0.016	0.793±0.020
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.020)	0.835±0.008	0.756±0.012	0.737±0.013	0.712±0.019	0.799±0.017
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.040)	0.814±0.005	0.744±0.015	0.731±0.014	0.710±0.017	0.778±0.020
	AdaTree(|ATE value|≥0.1, |SHAP value|≥0.050)	0.764±0.007	0.695±0.013	0.673±0.014	0.625±0.023	0.765±0.012

In multifactor logistic regression, sample power is closely related to interest variables [45]. If only the statistical characters of the studied data were considered, for the interest variables of FIB, GCS, and blood transfusion, the sample power of 550 samples could reach 0.987 (using PASS 15.05, OR: 0.632, Baseline probability: 0.31[11, 16], R-Squared: 0.292, alpha: 0.05, Alternative hypothesis: two-sided), 0.825 (OR: 0.736, Baseline probability: 0.31, R-Squared: 0.243, alpha: 0.05, Alternative hypothesis: two-sided), and 0.951 (OR: 2.054, Baseline probability: 0.31, Percent with X1=1: 0.44, alpha: 0.05, Alternative hypothesis: two-sided), respectively. But, for the interest variables such as MAP, Age, Glu, sample power would decrease to below 0.50. To maintain a high sample power for each interest variable, for example a sample power of 0.85, more than 165714 samples were needed (The variable 'Age' was taken as an example, using PASS 15.05, OR: 1.019, Baseline probability: 0.31, R-Squared: 0.285, alpha: 0.05, Alternative hypothesis: two-sided).

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Nevertheless, this research is more inclined to be a pattern recognition study. ARDS prediction was carried out only based on sample classification, and statistical features of predictors, as well as functional relationships between predictors and ARDS outcomes, were not needed to be considered comparatively.

There is no clear requirement of sample size for pattern recognition. In [46], it was indicated that samples should be several times the size of the data dimension, and the specific rate was determined by the optimization objectives. In engineering, a generally accepted option is that the number of samples should be 10 times the VC dimension of a machine learning model. For example, at least 280 samples are needed to train an SVM model with a linear kernel and 27 variables, and with an additional requirement of balanced samples. From this point of view, neural networks need far more samples as large training parameters are involved. However, with the help of some techniques, such as regularization and dropout, fewer samples are also acceptable. The VC dimension of the tree models is adjusted according to the number of leaf nodes [47]], and the tree models seemed to be able to reach the same sample power with a much smaller sample size [48].

The results of this study revealed that new machine learning models have the power to compete with conventional models in predicting the development of ARDS in patients with severe trauma. Tree models outperformed other machine learning models in both internal and external validation. However, according to the above analysis, it was also found that, being limited to the sample size, some machine learning models did not fully play their due roles. When the sample size is large, other machine learning methods, such as SVM and neural networks, may get comparable results. Compared to regression models, tree models have less interpretability. Therefore, in this study the SHAP method was provided to analyze the importance of each predictor. The essential variables in the prediction model were also uncovered.

The results of external validation in Table 4 also indicate that although the AdaBoost + DT model had the best performance, it was not stable. The prediction model training by the XGBoost algorithm was more stable and also had comparable results. If more stable results are needed, the XGBoost prediction model can be chosen.

The results of SHAP analysis showed that GCS, ISS, total protein, and blood glucose were the most important indicators in predicting ARDS in trauma patients. ISS [11, 17, 22], GCS [17], blood glucose [6, 20] and total protein [49] have been reported to be critical predictors associated with the development of ARDS in patients with severe trauma. And the findings in this study prove these studies. The results in Figure 2 and Figure 3 also indicate that blood sodium, creatine kinase, mean arterial pressure, AIS score, age, acute lung injury, APACHE-II score, heart rate, fibrinogen, prealbumin, shock, white blood cell count, smoking, pneumohemo-thorax, granulocyte and blood transfusion also had informational value in the prediction of ARDS. And these variables are secondary importance predictors. The results of casual inference in Table 5 show that whether drinking, respiratory rate, serum creatinine, prothrombin time, platelet, and emergency operation are factors with spurious correlations with the development of ARDS needs further investigations. These were inexplicit variables and the results in Table 6 prove that even if these variables were excluded in the model construction, a similar prediction performance could also be obtained.

In addition to the above findings, hypertension and diabetes mellitus were found to have no significant associations with the development of ARDS in patients with severe trauma. This is different from the research reports in [17] and [26]. It was also found that sex (P=0.063) was not significantly associated with the development of ARDS in patients with severe trauma. This was consistent with the reports in the literature [13, 22], and [23], but somewhat different from the reports in the literature [10, 15, 17, 18], and [26]. The reasons for these different findings may be different demographic characteristics, or the limitation of the patient proportion in this study.

This is a preliminary study and there are some issues that should be discussed and addressed before clinical application. Regarding the study design, this study was conducted in one medical centre. Whether the findings can be generalized to other populations needs a further study. The retrospective nature of the present investigation was also a restriction. Regarding prediction models, since there are many machine algorithms, maybe another one that performs better can be found further. Being limited to the sample size in this study, the power of some algorithms has not been fully exploited, especially the power of neural networks. Also being limited to the sample size and limited to biased data features, it was inevitable that biased estimates were obtained in the analysis of variable roles. These problems will be discussed in our further study. With respect to the ARDS prediction, the development of ARDS is time-varying and is not an absorbing state. The time-varying prediction of ARDS based on time-

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series models is another valuable question in a further discussion. Even so, in clinic, about 90% of patients with severe trauma developed ARDS 5 days after admission to the ICU and many patients even developed ARDS earlier [50]. For timely support, early detection of the risk of ARDS in patients with severe trauma is still of great importance.

In summary, this preliminary study established an acceptable prediction model for the development of ARDS based on predictors that were easily obtained. And this prediction model has the potential for the early detection of ARDS in patients with severe trauma. Relevant valuable factors for the development of ARDS were also uncovered.

5. Conclusions

The research objects were patients with severe trauma in the affiliated hospital of Zunyi Medical University from September 2021 to December 2022. Clinical data was collected and used to predict the development of ARDS early in patients with severe trauma. The results indicated that the collected data has a certain value in the prediction of ARDS. Intelligent tree models, particularly the Adaboost + DT model, can make good use of these data to predict the development of ARDS.

List of Abbreviations

ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; LR: Logistic regression; DT: Decision tree; SVM: Support vector machine; MLP: Multilayer perception; GBDT: Gradient boosting decision tree; XGBoost: eXtreme gradient boosting; SHAP: Shapley additive explanations; ROC: Receiver operating characteristic; AUC: Area under curve; CTWAT: Consultation time window after trauma; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; WBC: White blood cell count; Gran: Granulocyte; PT: prothrombin time; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; RBC: Red blood cell; TT: Thrombin time; HCO3: Serum bicarbonate; HCT: Haematocrit; PLT: Platelet; ChE: Cholinesterase; TBIL: Total bilirubin; TP: Total protein; ALB: Albumin; PA: Prealbumin; SCR: Serum creatinine, CK: Creatine kinase, CK-MB: Creatine kinase isoenzyme MB; AIS: Abbreviated injury scale; APC: Abdomen and pelvic cavity; ISS: Injury severity score; GCS: Glasgow coma scale; Glu: Blood glucose; APACHE: Acute physiology and chronic health evaluation; Pne-throax: Pneumohemothorax; COVID-19: Corona virus disease 2019; ATE: Average treatment effect.

Data Availability

The data used to support the findings of the study can be obtained from the corresponding author upon request.

Ethical Approval

The present study has been registered with the ethics code (KLLY-2021-060) in the ethics committee of the affiliated hospital of Zunyi Medical University.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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